

June 1998

The Medication Manager : A Theoretically Based Intervention to Improve Adherence to HIV Therapeutic Regimens

Laurie J. Andrews

Follow this and additional works at: https://opencommons.uconn.edu/uchcgs_masters

Recommended Citation

Andrews, Laurie J., "The Medication Manager : A Theoretically Based Intervention to Improve Adherence to HIV Therapeutic Regimens" (1998). *UCHC Graduate School Masters Theses 2003 - 2010*. 23.
https://opencommons.uconn.edu/uchcgs_masters/23

**The Medication Manager:
A Theoretically Based Intervention to Improve
Adherence to HIV Therapeutic
Regimens**

Laurie J. Andrews, BSN

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Public Health

at the

University of Connecticut

1998

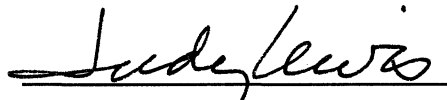
Approval Page
Master of Public Health Thesis

The Medication Manger:
A Theoretically Based Intervention to Improve Adherence to
HIV Therapeutic
Regimens


Presented by

Laurie J. Andrews, BSN

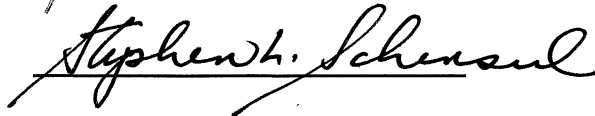
Major Advisor:

A handwritten signature in cursive script, appearing to read "Judy Lewis", written over a horizontal line.

Associate Advisor:

A handwritten signature in cursive script, appearing to read "Janet Fullard", written over a horizontal line.

Associate Advisor:

A handwritten signature in cursive script, appearing to read "Stephen H. Schensel", written over a horizontal line.

The University of Connecticut

1998

Dedication

**I would like to dedicate this to my dear friends,
Bill, Beth, Nicholas, John, and Victor, whom
I wish I could have helped with the knowledge
gained writing this thesis .**

ACKNOWLEDGEMENTS

I would like to express my appreciation to my advisors on this thesis, Judy Lewis, Steve Schensul, and Jerry Friedland. I would like to extend particular gratitude to Jerry for his patience with my absences from the AIDS program to complete this paper and for his mentoring in so many areas.

I would like to thank the staff at the AIDS program for their personal and professional support, especially my staff at the AIDS Clinical Trials Unit, Cyndi, Wanda, and Yvette, who showed up for work even when I wasn't watching and for their commitment to helping our patients adhere to their regimens. In addition, thank you to Jackie for keeping the paper moving and Mary Jo for her ongoing encouragement.

I would like to express special gratitude to Dr. Serafin Mendez-Mendez for his support and invaluable guidance and Carol Bozena for believing in me.

Lastly, I would also like to thank friends who coached me to finish this thesis, Lynn Mitchell for her persistence, Anne Parente, for her wisdom, and especially my partner, Loretta Gleason, for everything.

TABLE OF CONTENTS

Table of Contents	v
Dedication	iii
Acknowledgements	iv
List of Tables	vi
List of Figures	vii
Introduction and Objectives	1
Background-HIV Infection	4
Antiretroviral Therapy for HIV Infection	11
Medication Adherence in the Treatment of Chronic Diseases	19
Medication Adherence in the Treatment of HIV Disease	33
Behavioral Models to Guide the Practice of the Medication Manager	38
The Medication Manager	62
Conclusion	79
Appendix	82

LIST OF TABLES

Table 1	Conclusions of Pittsburgh MAC Cohort Study
Table 2	Approved Medications in the Treatment of HIV Infection
Table 3	General Strategies to Improve Adherence
Table 4	Surveys of Patient Adherence to Antiretroviral Therapies
Table 5	Reasons for Missing Doses of Antiretroviral Therapy
Table 6	Summary of Geneva Abstracts
Table 7	Abstracts by Category
Table 8	Central Issues and Findings that Emerged from Research Presented at The Twelfth World AIDS Conference, Geneva, Switzerland
Table 9	Phases of Illness and Health Studied under the Health Belief Model
Table 10	Significance Ratios for Sick-Role Behaviors, Prevention Behaviors, and Sick-Role/Prevention and Clinic Utilization Behaviors
Table 11	The Transtheoretical Model of Change
Table 12	Relevant Principles of Seven Behavioral Models in the Practice of Improving HIV Adherence

Appendix I: Review of Abstracts

LIST OF FIGURES

- Figure 1 The Health Decision Model**
- Figure 2 Preliminary Adaptation of IMB Model to Adherence**
- Figure 3 Medication Management for Non-Adherence to
Antiretroviral Therapies**

INTRODUCTION

Advances in the treatment of Human Immunodeficiency Virus have dramatically improved survival for those infected. Death rates from HIV infection declined by 47% from 1996 to 1997 and HIV dropped from the leading cause of death in 1995 to the fifth leading cause of death in 1997 in those in the 25-44 year age range (CDC, 1998). Antiretroviral medications developed within the last five years have resulted in suppression of viral replication, heretofore incomprehensible. However, this progress has been accompanied by a monumental challenge to those living with the infection as well as those involved in their treatment and enthusiasm for substantial and real progress has been subdued amidst fears that clinical gains may be short lived.

Combinations of medications used to treat HIV are commonly known as Highly Active Antiretroviral Therapy or HAART. These combinations are complex, requiring large numbers of pills and very specific instructions for their use. Unfortunately, HAART regimens, like other treatments for chronic diseases, also demand a level of a certain level compliance and incur serious consequences when adherence levels are too low. Non-adherence is a leading cause of the development of resistant virus and can lead to cross-resistance with other HIV medications rendering them ineffective. Not only are there personal consequences for the individual whose virus is no longer successfully controlled by his medications but the potential for transmission of resistant virus represents a serious potential public health concern.

The objectives of this paper are to develop an intervention to maximize HAART medication use. It is this author's belief that medication adherence requires a multidimensional and multidisciplinary effort. It is also her belief that it is difficult, if not impossible, to either evaluate or affect some patients' adherence in isolation from their daily life. The magnitude and gravity of the problem requires the development of a new member of the healthcare team, who would become the centerpiece of the adherence effort. This health professional would be specifically trained to evaluate knowledge, lifestyle, adherence behavior and motivation as well as to provide information, teach necessary skills, and serve as a liaison between the patient and provider.

The outcomes for this intervention are:

To support and improve antiretroviral medication adherence

- To demonstrate objective HIV disease therapeutic benefit by improvement in viral load, CD4 cell counts, and clinical outcome
- To decrease morbidity and mortality in those with HIV infection due to inconsistent pill taking behaviors
- To alleviate existing constraints and burdens placed on HIV providers and the health care system
- To lower HIV-related health care costs due to decreased hospitalizations, fewer emergency room visits, and decreased episodes of crisis health care management
- To reduce the incidence of antiretroviral resistant HIV and to decrease the potential for its transmission.

To this end, this thesis will present the fundamental principles of HIV and illustrate the relationship of inadequate viral suppression, non-adherence, and antiretroviral resistance. A review of the adherence literature, as well as literature on behavioral models will then be assimilated to develop the practice and principles of a

medication manager. A curriculum to train medication managers will be proposed and a description of responsibilities of this new health professional will be presented.

HIV INFECTION

HIV Pathogenesis: How the Virus Works

HIV, like all viruses, is totally parasitic. It cannot reproduce independently and must invade a host cell and use that cell's machinery in order to replicate. The process of viral replication in various host cells in the body is called the Viral Life Cycle. The single strand of RNA in the core of the virus must be transcribed into DNA in order to infiltrate the host cell's DNA and for viral replication to occur. This transformation from viral RNA to viral DNA occurs with the help of the enzyme contained in the viral core called reverse transcriptase. The viral DNA is then able to infiltrate the host cell's DNA to usurp the host's genetic machinery in order to replicate its own genetic blueprint. The long chain of viral products that are produced in the cell nucleus must then be cut and reassembled to construct a new viral particle. This is done with the help of the viral protease enzyme. The host cell is thus transformed into an HIV virus factory, producing viral proteins instead of the cell's normal regulatory proteins.

Relentless viral replication in susceptible cells is the primary mechanism of immune system destruction in HIV infection. Ho (1995), Wei (1995), Coffin (1995) and others have demonstrated a highly dynamic process with a rapid turnover of virus, even in asymptomatic patients. The number of virions (viral particles) present in the body at a given time is a result of the battle between the virus and the immune system. The number of virions detected is referred to as the viral load.

The Surrogate Marker for Effective Medication Adherence: Viral Load

The value of following a patient's viral load has been well-established (Mellors, 1996, Mellors, 1997). To underscore the role of the amount of virus in the body Coffin introduced the analogy of a train approaching a cliff, in which the CD4+ cell count is the distance to the precipice and the viral load is the speed of the train (Coffin, 1996). The total amount of virus detected on viral load testing is in fact a surrogate for how quickly the virus is actually replicating. How quickly the virus is replicating determines how quickly valuable CD4+ lymphocytes are being destroyed and how hard the immune system must work to replenish the store of immune cells. Over time, the T cell replenishing system tires, whole populations of T cells, like memory cells, which recognize antigens, are wiped out and HIV gains control.

Mellors et al. (1996, 1997) analyzed viral load data from the Multicenter AIDS Cohort Study (MACS) to demonstrate the ability of viral load, with and without CD4+ cell counts, to determine the risk of progression to AIDS and death.

In his analysis Mellors (1996) used frozen and saved plasma specimens from different timepoints during the MAC study to obtain viral load measurements. He added the viral load data to CD4+ cell results, and to clinical endpoint and survival data from 180 of the 209 HIV-infected gay or bisexual men enrolled in the Pittsburgh MACS site. The relationship between baseline viral load (the viral load performed on saved specimens that were obtained at the patients first visit) and baseline CD4+ T cell counts were examined. The results of Mellors research are summarized in Table 1.

Table 1: Conclusions of Pittsburgh MAC Cohort Study: (Mellors et al., 1996).

- The risk of AIDS and death was directly related to plasma viral load.
- There was a significant increase in the rate of progression to AIDS in those with higher viral loads.
- There was a significant difference in median time to death in those with $\leq 10,190$ copies versus $\geq 10,190$ copies per ml.
- Individuals with a 3 fold higher viral load face a 1.5 times greater risk of death within 10 years.

Measures of viral load are generally accepted as markers of viral control, successful treatment, or HIV treatment failure. Viral load measurements can now detect viral levels to as low as 20 copies per milliliter of plasma. The succession of measurements of viral load provides both the individuals with HIV and their providers of care with a snapshot of viral activity in a given moment. High viral loads are indicative of a high rate of viral replication.

Numerous clinical trials have shown that effective therapeutic regimens drive virus to levels below the level of detection in plasma, which occurs when viral replication is inhibited. (Wong, 1997). However, it is still premature to know what the natural history of viral replication over time will be in patients who are adherent. It is hoped that natural history can be influenced by an ongoing assault with potent antiretroviral therapy. However, evidence has surfaced that even in the presence of potent antiretroviral therapy, replication competent virus can still be found in lymph nodes and resting cells. This casts a cloud of uncertainty on current successes. Currently, we have reason to believe that viral levels which rise to detectable levels after successful suppression point to medication failure. HIV medication failure is principally a function of the development of viral mutations, arising from the virus' natural instinct to survive. Given that adequately suppressed virus cannot mutate and that partial suppression favors mutations and the development of resistance,

increases in viral load have also become recognized as a flag for poor adherence to medication regimens. It is with this awareness that the field of medication adherence in HIV treatment has flourished.

How Resistance Happens

As stated previously, viral genes carry the blueprint to direct the formation of HIV specific proteins (long chains of amino acids), including enzymes, that are contained in a single HIV particle. (Cooper, 1997). The nucleotide sequences contained in the genes specify the order in which the amino acids are incorporated into proteins. This configuration is the basis for medication development.

Studies published in 1995 provided valuable insight into the kinetics of HIV as well as the mechanisms of viral variation and resistance. In particular, two observations that year have direct bearing on our understanding of resistance; first that HIV replicates at a remarkable rate (Ho et. al, 1995; Wei et. al, 1995). An estimated ten billion copies of virus are made each day (Coffin, 1996). The second relevant observation is that a key enzyme in viral replication, reverse transcriptase, lacks an essential proofreading mechanism and is thus very error prone in its replication efforts. It has been estimated that each time the virus replicates at least one amino acid substitution occurs, changing the virus slightly from its progeny each replication cycle (Coffin, 1995).

Therefore, viral variation and the resultant genetic diversity in HIV infection are a natural consequence of both high levels of viral replication and an error prone reverse transcriptase enzyme. In fact, the higher the viral replication rate the greater the number of

errors made. Even in the absence of drug therapy viral mutation is inevitable given the nature of HIV dynamics.

Generally, these mutations represent only a small percentage of all the virus found in one individual. Early on in infection there is little evidence of mutation. This virus is said to be “Wild Type” or in an unmutated state, like that found in nature. If mutated virus is not amplified under conditions of drug pressure, it may never be recognized, since it will exist only as a small percentage of a larger species. (Wainberg and Friedland, 1998) Over time, however, if the virus is allowed to replicate the virus becomes increasingly diverse as ongoing changes become incorporated into new virus. It is precisely these mutations that result in changes in the viral susceptibility to a particular drug. Substitutions in the order of amino acids contained in the viral enzymes, protease and reverse transcriptase, confer reduced susceptibility to the classes of medications, protease inhibitors and reverse transcriptase inhibitors.

Transmission of Resistant Viral Strains

The initial report of transmission of HIV, resistant to AZT, was published in 1993 (Erice et al.). In a more recent international study of viral resistance involving Swiss, Australian, and US patients, 8-11% of Swiss and Australian patients and 6-8% of American patients were resistant to AZT upon seroconversion (Mayers, 1995). Transmission of resistance to 3TC and nevirapine has also been reported (Conway, 1997). In a recent study presented at the Twelfth World AIDS conference Hecht (1998) reported the transmission of virus resistant to AZT, 3TC, indinavir, ritonavir, saquinavir, and nelfinavir, detected in a newly infected, untreated individual. This confirms the assertion of Wainberg and

Friedland, (1998) that transmission of virus resistant to all classes of antiretroviral agents is likely.

The Effect of Antiretroviral Treatment on Viral Replication and Resistance

Potent combinations of antiretroviral therapy offer the greatest opportunity for durable suppression of viral replication. Several important discoveries have been made which support this hypothesis. First, the higher the trough level (the level at the lowest point) of plasma concentrations of medications, the more slowly resistance is likely to emerge (Molla, 1996). The second is that the lower the viral load is driven, the longer the viral response to medication will last (Kempf, 1998).

In a patient who is who is taking medication as prescribed (adherent) and whose viral replication is minimal, viral mutations are also minimal. Conversely, in a patient who is not taking their medication adequately, there is ongoing replication and consequently increasing amounts of mutations develop.

Partial treatment favors the development of mutations by inhibiting virus that is sensitive to the medication and giving drug-resistant strains a competitive advantage. In this way, medication is said to exert selective pressure on the virus, allowing one or more formerly uncommon, mutated HIV strains to multiply while inhibiting dominant natural strains that are sensitive to treatment.

When antiretroviral medications are developed they are designed to inhibit the virus replication by interacting with the virus at a particular point, called the active site. The active site is located in key positions in the protease or reverse transcriptase enzymes. When mutations occur in the active site of the virus, the effectiveness of their corresponding

medications, reverse transcriptase inhibitors or protease inhibitors, is lost. Non-adherence to antiretroviral therapy is the shepherd for this cascade of event.

ANTIRETROVIRAL THERAPY FOR HIV INFECTION

The Challenges in HIV Medication Regimens

The challenge of HIV medication adherence is set against a backdrop of harsh realities about the regimens themselves. Numerous studies have shown that successful inhibition of HIV viral replication requires not single therapy but combinations of a minimum of three medications (Hammer, 1997). An individual may have to consume as many as 20 to 25 pills, to be taken each day, often divided over two or three doses at different times during the day. Besides the large number and frequency of pills, there are also other factors, which make current medication options difficult to take. Individuals who are being treated for HIV infection have to contend with a plethora of medication side effects, some of them life threatening, disfiguring, or reducing quality of life. Current formulations of HIV medications also have numerous interactions with other medications, are altered by the presence or absence of food and some even have specific storage requirements. This obligates patients to adhere to strict instructions concerning the timing of their medications and forces individuals to structure their lives around their pill taking. The ever-present reality of drug interactions demands a strict awareness and knowledge of the potential conflict with other seemingly harmless medications. Conflicts with other medications competing for the same mechanism of drug metabolism can either lead to inadequate levels of one of the medications or dangerously high levels of one of them. There are serious consequences in either case; one facilitating sub-optimal drug levels and increased viral load and the other increasing the likelihood of toxicity.

Recognizing the delicate balance between toxicity and adequate therapeutic medication levels, difficult medication instructions must be followed precisely. The process of drug development aims to identify the most efficacious and safest medication doses but this also results in medications which have a narrow therapeutic range. A minimum amount of medication must be ingested in order to assure adequate therapeutic blood levels. For example, in hypertension it has been determined that blood pressure begins to fall only when patients take more than 80% of their medication. Based on hypertension experience many surveys of HIV medication adherence have used the 80% cutoff as a significant measure of adherence. In fact the question of how much adherence is enough in HIV treatment has not been answered but is assumed to be an unequivocal “a lot” (Woodward et al., 1998).

The psychological barriers to HIV medication taking are complex and an in-depth review could be the subject of an entire thesis. However, there are several issues worth mentioning. One issue is that pill taking is in itself a constant reminder of the devil that threatens the lives of people with HIV, presenting those infected with the intrinsic challenge of facing their disease on a daily basis. Those who have not integrated HIV successfully into their lives may have difficulty accepting the burdens and reminders in treatment. In a study presented at the Twelfth World AIDS Conference in Geneva, Switzerland psychological well being was explored as a factor in medication adherence. The study concluded that “feeling comfortable and well cared for” and having a “meaningful life” are factors associated with medication adherence (Holzemer et al., 1998). It has also been theorized that an understanding of the complex relationship of individuals with HIV to their environment must be understood in order to understand their compliance with care,

including medication adherence, (Bennet et al., 1998).

Thus, those with HIV are expected to take their pills faithfully, in spite of the enormous challenges presented by complex regimens, in the face of environmental and psychosocial barriers and despite the nature of human failings.

Antiretroviral Therapy Mechanisms of Efficacy

It is well known that the efficacy of any therapeutic regimen depends on adequate blood levels of individual medications producing a desired physiologic response. The efficacy of antiretroviral regimens used to treat HIV infection depends on adequate antiretroviral levels to inhibit viral growth and minimize the consequences of HIV disease. Adequate suppression of the virus interrupts the viral life cycle and ultimately diminishes the rate of infection of uninfected cells in the body. Suboptimal levels of antiretroviral medication lead to incomplete viral suppression and invites the outgrowth of less common mutated viral species. Although there are a number of variables which impact achieving adequate blood levels, such as absorption and drug interactions, adherence remains a necessary element in the equation.

Profile of Highly Active Antiretroviral Therapy (HAART): The Landscape of Viral Regimens

There are currently 15 approved medications for the treatment of HIV infection. These medications, their dosing, side effects and special instructions are found in Table 2. The addition of protease inhibitors and non-nucleoside reverse transcriptase inhibitors to antiretroviral options has dramatically increased regimen complexity. A number of these

medications have specific gastric requirements (full stomach versus empty stomach) and use the p 450 pathway for liver metabolism. . The liver enzyme p450 is responsible for the metabolism of many drugs. Medications that are described as an inducer of p450 can increase the metabolism of other drugs and medications that are an inhibitor of p450 can slow the metabolism of other drugs that share the same metabolic pathway. This translates to slower excretion (increasing exposure to the drug) or more rapid excretion (inadequate amount of exposure to the drug). Drugs that induce or inhibit metabolism must be taken cautiously with other medications that are metabolized in the same manner. Table 2 is followed by some typical antiretroviral regimens.

Table 2: Antiretroviral Medications Used in the Treatment of HIV Infection:

Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Adult Daily Dosing	# Pills/Day	Most Common Side Effects	Special Instructions	Interactions
AZT (Retrovir)	One 300 mg tablet BID	2	Bone marrow suppression, anemia, nausea, myopathy		
3TC (Epivir)	One 150 mg tablet BID	2	Headache		
AZT/3TC (Combivir)	One 150-mg/300 mg tablet BID	2	Bone marrow suppression, anemia, nausea, headache myopathy		
ddC (Hivid)	One 0.75 mg tablet TID	3	Peripheral neuropathy, stomatitis		Cannot be taken with ddi or with magnesium/aluminum containing antacids
ddI (Videx)	Two 100 mg tablets BID	4	Peripheral neuropathy, pancreatitis, nausea	Take on an empty stomach	Reduces levels of delavirdine, and all protease inhibitors
d4T (Zerit)	One 40 mg capsule BID	2	Peripheral neuropathy		
Abacavir (Ziagen)	One 300 mg tablet BID	2	hypersensitivity reaction- fever, nausea, vomiting, malaise, rash		

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Adult Daily Dosing	# Pills/Day	Most Common Side Effects	Special Instructions	Interactions
Delavirdine (Rescriptor)	Four 100 mg tablets TID	12	Rash, headaches	With or without meal; requires acidic ph	Moderate enzyme inhibitor. Take one hour apart from ddI and antacids. Increases levels of indinavir
Efavirenz (Sustiva)	Three 200 mg capsules QD	3	Rash, light-headedness, dizziness, feeling disconnected, pancreatitis		Moderate enzyme inducer. Crixivan levels reduced, nelfinavir levels increased
Nevirapine (Viramune)	One 200 mg tablet BID	2	Rash (stevens johnson can occur); hepatitis		Moderate enzyme inducer. All protease inhibitors affected by nevirapine
Protease Inhibitors (PI)	Adult Daily Dosing	# Pills/Day	Most Common Side Effects	Special Instructions	Interactions
Indinavir (Crixivan)	Two 400 mg capsules every 8 hours	6	GI, nephrolithiasis, nephrotoxicity, hyperbilirubinemia	Take on an empty stomach 1 hour before or 2 hours after a meal. Drink at least 6 eight oz of water per day. Requires acidic ph	Moderate enzyme inhibitor. Levels increased by nelfinavir and delavirdine. Levels reduced by nevirapine, efavirenz, and ddI (take 2 hours apart)
Saquinavir Soft Gel Caps (Fortovase)	Six 200 mg capsules TID.	18	GI, headache, increase liver enzymes	Take within 2 hours of a full meal. Has no antiviral effect if taken on an empty stomach	Mild enzyme inhibitor. Levels increased by ritonavir, nelfinavir, delavirdine, indinavir. Levels reduced by nevirapine

Protease Inhibitors (PI)	Adult Daily Dosing	# Pills/ Day	Most Common Side Effects	Special Instructions	Interactions
Ritonavir (Norvir)	Six 100 mg capsules BID	12	GI, paresthesias, taste perversion, increased liver enzymes	Take with meals. Grapefruit juice increases levels. Store in refrigerator	Potent enzyme inhibitor. Levels increased by ritonavir, nelfinavir, delavirdine. Reduced by ddI (take 2 hours apart)
Saquinavir (Invirase)	Three 200 mg capsules TID	9	GI, headache, increase liver enzymes	Take within 2 hours after a meal. Do not take on an empty stomach	Mild enzyme inhibitor. Levels increased by ritonavir, nelfinavir, delavirdine, indinavir
Nelfinavir (Viracept)	Three 250 mg tablets TID	9	Diarrhea	Take with a meal or a light snack	Moderate enzyme inhibitor. Increases levels of saquinavir and indinavir. Efavirenz increases levels

Examples of Antiretroviral Regimens Currently in Use:

1. One PI and 2 nRTIs
Example: AZT/3TC/indinavir (8 or 14 pills per day) (TID regimen)
Example: ddI/d4T/ritonavir (13 pills per day) (BID regimen)
2. One NNRTI and 2 nRTIs
Example: efavirenz/d4T/3TC (9 pills per day) (BID regimen)
3. Two PIs with 1 or 2 nRTIs
Example: ritonavir/saquinavir/ddI/d4T (27 pills per day) (TID regimen)
4. One PI and 1 NNRTI with 1 or 2 nRTIs
Example: nelfinavir/efavirenz/combivir (14 pills per day) (TID regimen)
5. Three nRTIs.
Example: d4T/3TC/abacavir (less potent regimen) (6 pills per day) (BID regimen)

MEDICATION ADHERENCE IN THE TREATMENT OF CHRONIC DISEASES

What Is Adherence And What Have We Learned About Adherence and Non-adherence Thus Far?

“The physician should keep aware of the fact that patients often lie when they state they have taken certain medicines” (Hypocrites, circa 400BC)

The extent to which a person's behavior coincides with medical or health advice is generally referred as adherence or compliance (Haynes, 1979). For a precise distinction between the two, Webster's Dictionary was employed. Adherence implies “attachment to a person or cause; sticking fast, to stay firm in supporting or approving”. Compliance, on the other hand is defined as “giving in to a request, wish, or demand; acquiescence; a tendency to give in readily to others; yielding, submissive, or obedient”.

Given the implication of control that is connoted in the word compliance and the evolution in health care toward patients as consumers of services, rather than passive recipients of doctors orders, one can see how adherence seems to have emerged today as the more appropriate term. Some have even gone so far as to describe the effort as a therapeutic alliance, but for the purposes of this paper adherence will suffice. Making light of this debate however, is not meant to detract from the intention of this author to contribute to the notion that the effort is necessarily a partnership. In this partnership the patient contributes expertise on his life and worldview and the provider contributes expertise on the scientific basis for treatment.

Even if there was agreement on what it should be called, our current definition of adherence is quite subjective and generally implies that patients must take all their medications, all of the time. Several studies in fact have shown that 100% compliance is not always necessary. Friedland (1998) uses the term “pharmacologic forgiveness” to describe therapies that are chronically administered and are known to have a long duration of effect after dosing, allowing for lapses in adherence. Friedland also asserts that these medications may also have a large therapeutic-toxic ratio. The definition of adherence could be clearer if we consistently knew the point below which the desired therapeutic result is unlikely to be achieved. In one study conducted to determine this, Fletcher demonstrated that blood pressure falls significantly when patients take more than 80% of their medication (Fletcher, 1974). In an earlier study, Markowitz demonstrated that oral rheumatic fever prophylaxis could be achieved if children took at least 33% of their penicillin (Markowitz, 1970). Unfortunately, most medications are not developed with minimum requirements in mind and therefore cut off points are rarely available. Even when studies have attempted to define minimum exposure necessary for adequate blood level, results often did not coincide with levels needed for clinical effectiveness (Gordis, 1976).

Although for antiretroviral therapies there has not been concrete documentation of minimum adherence, inferences have been made. It is also possible that different antiretrovirals with differing characteristics may not all share the same threshold. Authors of a report of the effects of high doses of the protease inhibitor saquinavir noted that in a small subgroup of patients studied for adherence and mutations, interruptions in dosing for as short as three days resulted in immediate viral load increases (Schapiro et al., 1996). Significantly, viral load increases occurred even before mutations appeared in the plasma of

the study patients. The authors interpret their findings to suggest a relationship between even brief periods of non-adherence and increases in plasma RNA levels. Unfortunately, a failing of this study was the lack of accompanying pharmacokinetic data, which would enable us to understand pharmacokinetic factors of increased viral loads.

Whether it is referred to as adherence or compliance, the medical literature is rich in information concerning the topic for a variety of chronic diseases including hypertension, diabetes, asthma, arthritis, and cardiovascular disease. In fact, a recent medline search in preparation for this thesis netted 15,650 articles since 1966, under the search topic adherence or compliance.

Documentation of the Problem: Prevalence Rates of Non-adherence

The incidence of non-adherence varies across circumstances. Non-adherence rates for prevention regimens range 30-40% overall, while rates for short term curative regimens are a slightly better 20-30% (Haynes, 1979). The rate of non-adherence for chronic diseases or long term regimens consistently averages around 50% (Sackett and Snow, 1979; Becker, 1985; Eraker, Kirscht, Becker, 1984). A striking example of non-adherence is offered by Vincent (1971) who studied patients being treated for glaucoma. These patients were told that “they must use eye drops three times a day or they would go blind.” Only 42% of the patients took enough medication to prevent blindness. At the point where patients were becoming blind in one eye, their adherence only improved to 58%, leading some to conclude that non-adherence is a form of self-destructive behavior (Faberow, 1986).

Given that we often do not know what constitutes adequate adherence we are left with a subjective and often ambiguous term. Having said that, non-adherence takes many

forms, each presenting the provider with a unique challenge in caring for their patient.

Non-adherence is an issue that transcends all health-related behaviors including medication taking, keeping medical appointments and health related behavioral changes. For the purposes of this paper, only non-adherence to medications will be reviewed in detail. Even within medication non-adherence the following deviations have been described:

- 1) Not filling a prescription or filling a prescription late, causing an interruption in dosing (also known as a “drug holiday”)
- 2) Not taking the correct medication dose
- 3) Not adhering to gastric requirements (with or without food)
- 4) Not adhering to instructions concerning concomitant medications
- 5) Skipping doses
- 6) Taking doses at the wrong time
- 7) Not finishing the prescription as instructed

Influences on Adherence: Factors and Barriers Contributing to Non-Adherent

Behavior in Chronic Diseases

The factors, which explain variances in adherence, have been the subject of much research over the years. Haynes (1976) conducted a comprehensive review of more than 200 potential variables in relation to adherence. Taylor et al. (1978) identified risk factors of noncompliance in antihypertensive therapy and Haynes (1979) followed with a second comprehensive review of determinants of noncompliance in which he detailed determinants identified in 185 journal articles. Determinants of adherence are generally clustered into several main categories: medication factors; provider factors; disease factors and patient factors. Meichenbaum and Turk (1987) noted that although these factors are generally discussed independently they are substantially interrelated. The findings of the large comprehensive reviews cited above and others are summarized below:

Medication Factors

Duration of Therapy

The duration of treatment has been found to be negatively associated with adherence, decreasing with increasing duration on therapy. Charney (1972) reported that diabetics who had been treated for 1-5 years demonstrated a 30% error rate which rose to an 80% dosage error rate in patients who had been treated for more than 20 years. Abernathy (1976) reported that 19% of patients treated for mild hypertension discontinued therapy in the first 2 years. Furthermore, the comparison of a 50% medication adherence rate for long-term treatment versus 77% rate of adherence for short term treatment is highly supportive of the influence of duration of treatment (Haynes, 1979).

Regimen Complexity

As a regimen becomes more complicated, compliance declines (Becker and Maiman, 1980, Haynes, 1979). Hulka et al. (1975) demonstrated that patients with diabetes or congestive heart failure had less than 15% medication errors when one drug was prescribed; 25% medication errors when two or three drugs were prescribed; and had greater than 35% when five or more drugs were prescribed. In Haynes' 1979 review, eleven studies were reported to have found a significant negative association with the number of drugs in a regimen (Brand et al, 1977; Clinite, 1969; Davis, 1963; Francis et al., 1969; Hemminki, 1975; Hulka, 1966; Latiolais, 1969; Malahy, 1966; Neely, 1968; Parkin, 1976; and Weintraub, 1973). Medication regimens are further complicated by multiple dosing schedules. Malahey (1966) and Brand (1977) demonstrated that the number of doses per day was a stronger predictor of non-adherence than number of pills per day. The notion of three times a day versus every 8 hours can be confusing even applied to a single

medication. This confusion can be multiplied by the addition of several drugs. Svarstad (1976) reported that three out of four times patients were not given specific instructions concerning dosing. Meichenbaum (1987) suggests that complex regimens overwhelm people who then use one or more non-adherent behaviors to cope.

Side Effects

There is little support in the general chronic disease literature to relate medication side effects to adherence. In the Haynes review there were no studies reporting significance for this variable further in studies of patient surveys of non-adherence Haynes (1979) summarized that only 5-10% of patients even mentioned side effects as an issue and none felt it was an important factor in non-adherence. However, side effects will be addressed more fully as a determinant of antiretroviral adherence in HIV infection.

Regimen Intrusiveness

Meichenbaum (1987) asserts that the demands placed on the patient's life, disruptions in daily routines and lifestyle, represent an important impediment to taking medication. The degree to which behavioral change is required is determined by a combination of medication factors and the patient's perception of the inconvenience of the regimen.

Patient Factors

Demographic Features of Patients

The literature does not support assumptions that adherence can be predicted by any demographic variables. Haynes (1976) reviewed studies of demographic characteristics and identified few studies that found positive associations with medication adherence using a scoring system that assigned ascending numerical values for progressively rigorous

methods. Far more studies found no association including factors such as social class, age, sex, education, and marital status.

Social Isolation and Social Support

The positive influence of social support and the negative influence of social isolation have been well documented. Oakes (1970) reported that patients who believe that family members expected compliance were more likely to comply. In a study conducted by Porter (1969), living alone was the most significant influence on adherence among chronically ill medical patients. In a review of 19 studies conducted by Baekeland and Lundwell (1975) low social support was a significant finding in each study reviewed. Stability and family support also correlated with adherence (Becker and Green, 1975). Thus, the availability of patient support should be discussed and, when possible, a family member or close friend should be included in the adherence process.

Patient Involvement

Various behavioral models empirically support active patient participation in planning and decision-making concerning treatment. Inclusion of the patient as a collaborator increases commitment and enhances motivation. The patient is more likely to adhere when they set their own goals and feel supported in their efforts, rather than judged for their failures.

Health Beliefs and Attitudes

The Health belief model developed by Rosenstock suggests that patient's perceptions of the severity of their illness and the benefits of the treatment influence health behavior. Taylor et al. (1978) demonstrated that the relationship of health beliefs to behavior seems to reach statistical significance after patients have been treated over time.

Health beliefs of steelworkers were assessed during blood pressure screening and again after 6 and 12 months of therapy. Beliefs before treatment were unrelated to adherence behavior at 6 and 12 months after therapy. However, after treatment, significant correlation was documented for beliefs concerning severity of illness, negative attitudes toward drug taking, and the worry that illness would lead to dependency. This suggests the importance of discussing health and treatment beliefs after the patient has had experience with the regimen.

Locus of Control

Individuals who view themselves in control of their lives, motivated by an internal locus of control, are more apt to comply with treatment. Studies of hypertensive (Lewis et al. 1978), and hemodialysis patients (Poll, 1980) demonstrate a positive association with adherent behavior and a sense of internal control. Non-adherence may also represent the patients attempt to gain back control over the illness or the treatment (Meichanbaum, 1987).

Knowledge and Understanding

Knowledge does seem to influence decisions but the literature is conflicting on whether or not it has a significant relationship to medication adherence. Studies have reported varying results that range from no relationship (Kirscht et al., 1981, Cummings et al., 1982) to a positive effect (Rosenberg, 1971, Maiman et al., 1979). One fundamental problem in evaluating the relationship of knowledge to behavior is that knowledge is an ambiguous and inconsistently used term. Also, information is often “given” in terms that patients may not understand, in a language that patients may not understand or in the absence of any measure of comprehension. Misunderstanding has been demonstrated for dosing terms such as “every 6 hours” (Mazzullo, 1976), and terms such as “evening” or

“with food” may be misinterpreted. Svarsted (1976) reported the results of a study to analyze the influence of information given at a neighborhood health center. Results highlighted many problems in the “giving” of important medication information. Patients were prescribed medications without accompanying verbal or written information and patients were rarely given information about regimen dosing and duration. In this study 17 % of patients with poor understanding of their regimen were adherent versus 60 % of patients with accurate information.

Patient-Provider Factors

Relationship with Provider

Several aspects of the patient’s relationship with the provider have been shown to significantly influence adherence. Better adherence is associated with physicians giving explicit, clear, and appropriate instructions, and timely positive feedback (Davis, 1968). The length of time a physician spends with a patient also has a positive effect. Patients who feel satisfied with their visit and have a provider with whom they can communicate have better adherence (Meichenbaum, 1987). Adherence is compromised when patients feel their expectations are not met or they experience the physician as unfriendly, not empathic or rushed (Davis, 1968). Strauss et al. (1984) asserted that there is a fundamental discrepancy between the patient and provider, maintaining that providers judge medication regimens on their medical worth and patients judge regimens on a social basis. Providers who lack an appreciation of the impact of medication taking on a patient’s life may find themselves alienated from their patient.

Increased Patient Supervision

There is a clear and strong correlation between the degree of supervision and adherence. Wilbur (1969) demonstrated the benefit of regular home visits to hypertensive patients by a public health nurse. Eighty-eight patients were followed for two years. During this time the percentage of patients who accepted treatment for their hypertension increased from 25% to 85%. Relevant findings on the influence of increased patient supervision are that adherence improves when the frequency of out patient visits is increased, when home visits are added and when the patient's family is involved in supporting the their adherence.

Disease Factors:

Adherence is more likely for short term, symptomatic illness (O'Brien, 1992). Patients with chronic illness must adjust to the fact that no matter how diligent they are about compliance they will never be rewarded with a cure (Cameron and Gregor, 1987). When chronic illness is asymptomatic the patient must arrive at health decisions without the "benefit" of cues, which provide motivation for treating illness. Taylor (1978) and others (Meichanbaum and Turk 1987) assert that adherence is lower in the absence of symptoms, which serve as a medication reminder. Taylor (1978) reported on 416 patients surveyed on their antihypertensive adherence. Fifteen percent revealed "they had stopped taking medication because they felt they did not need it."

A Review of Strategies to Improve Medication Adherence in Chronic Diseases

Although correlates of adherence have been identified, the literature is surprisingly weak and sometimes contradictory on effective measures to improve adherence. A review of the hypertension data from 1960-1991 demonstrated that despite years of efforts to

improve adherence to antihypertensive medications only 29% of the 50 million people in the U.S. who are hypertensive have their blood pressure controlled (Burt, 1995). Adherence to long term regimens is more difficult to achieve than for short-term regimens and is complicated by the evidence that adherence declines when interventions are withdrawn (Harris, 1971). Reviews of medication adherence to regimens for chronic diseases emphasize that no single strategy is effective in improving adherence.

Behavioral modification techniques have been employed with success in changing behavior. Tailoring is the process of fitting prescribed regimens to patient routines and circumstances. Tailoring recognizes the needs and the uniqueness of the individual and addresses issues of disruptions in lifestyle. Contingency contracting refers to the process of negotiating on specific behaviors and formalizing a commitment to following them. Reminders are a useful cue for pill taking and may range from phone calls to new electronic beepers programmed for dosing times. Reminders may be especially helpful for asymptomatic patients who are not cued to take their medications by symptoms.

Haynes (1976) demonstrated the utility of these modalities in an intervention for improving antihypertensive adherence using behavior modification principles. The intervention included self-monitoring, tailoring of medications to patient schedules and positive reinforcement. They concluded that there was a 21% increase in adherence in the intervention group compared to a 1% decrease in controls over time.

In a review of adherence interventions, Haynes (1987) stresses the need for multifaceted interventions which may include: enhancement of social support, written instructions, patient self-monitoring, contingency contracting, rewards or reinforcement, group discussions, and increased supervision. In a later review by Haynes et al. (1996),

randomized trials of adherence interventions which met a rigorous standard were evaluated. Criteria for inclusion of the studies in the Haynes review required that the study used one or more measures of adherence, one or more measures of treatment outcome, at least 80% follow-up of each group studied, and at least 6 months of follow-up for long term studies. Between the years of 1993 and 1995 four medline searches were performed and 1553 citations were reviewed. Two hundred and fifty two articles were deemed worthy of full review however, only 13 randomized clinical trials met all the criteria for inclusion in the analysis. Ultimately, the authors concluded that even the most effective interventions did not lead to substantial improvements in adherence when used alone.

Four of the interventions reviewed by Haynes produced significant influences on adherence as well as outcomes:

Bailey (1990) demonstrated positive effects on the adherence of 132 patients taking asthma medications through the combined interventions of a pamphlet, workbook, counseling, phone follow-up, support group and reinforcement of adherence. Colcher (1972) improved the adherence of short-term treatment for strep throat with counseling plus written instructions on how to take pills. Logan (1979) showed a significant effect on adherence with worksite nurses, tailoring medication regimens, self-monitoring of blood pressure and rewards for higher adherence and lower blood pressure. Strang (1981) improved adherence with family therapy for patients with schizophrenia. Other interventions improved adherence but did not meet the rigor of improving outcomes. These included decrease in medication frequency (Baird, 1984) and other combinations of interventions which included tailoring and increasing support and supervision.

In a recent meta-analysis, Roter et al. (1998) reviewed 153 studies of measures to improve adherence. She classified interventions by theoretical basis in categories of educational, behavioral and affective interventions. Roter concluded that each of the interventions had a small effect size. Roter (1998) concurs with Haynes' conclusion that "no single strategy or programmatic focus showed any clear advantage compared with another." Significantly, the most powerful interventions included the combination of three modalities: educational, behavioral, and affective. She cites the need for much more information giving and positive talk and less questioning. She also reaffirms that the length of the visit and the degree of collaboration with the patient are important characteristics of adherence support.

Table 3 summarizes adherence intervention strategies and principles from the chronic disease literature.

STRATEGIES FOR IMPROVING MEDICATION ADHERENCE

Table 3: (Adapted from Miller, 1997)

STRATEGIES:	REFERENCE
EDUCATIONAL	
Knowledge is a necessary but not sufficient component of behavior change	Eraker, 1984
Information should be given in clear non-technical language accompanied by written instructions which include information on dosing frequency, medication duration, potential side effects	Eraker, 1984
Combined use of written and verbal instruction may enhance adherence	Pratt, 1995
Return demonstration of information (i.e. how to take pills) helps to evaluate comprehension	Miller, 1995
BEHAVIORAL	
Tailoring treatment to habits and not habits to treatment improves adherence	Haynes, 1976
Simplifying regimens to once or twice daily and eliminating unnecessary medications increases adherence	Rudd, 1995
Adherence enhancement requires the use of a combination of behavioral interventions (i.e. contracting social support, goal setting)	Haynes, 1987
Maintenance of most behaviors declines over time; constant questioning and follow-up are essential to assure adequate adherence	Dunbar-Jacob, 1991
PATIENT-PHYSICIAN COMMUNICATION	
Patient satisfaction with the provider is correlated with adherence	Haynes, 1976
The likelihood of adherence is increased when the patient's expectations of a visit are matched by what actually occurs	Becker, 1985
Sincere warmth and concern, responding to questions, desire to influence adherence, and spending additional time with patients are important physician attributes	Pratt, 1995
Physician awareness and training about adherence have positively influenced rates of patient adherence	Svarstad, 1976
Increasing supervision of patients through home visits, more frequent appointments, etc. improves adherence	Wilber and Barrow, 1969.
COMBINATION STRATEGIES	
Combination interventions which include an education, behavioral, and affective components have the strongest effect on adherence	Rotor, 1998

MEDICATION ADHERENCE IN THE TREATMENT OF HIV DISEASE

The literature on adherence to antiretroviral therapies in the treatment of HIV disease is relatively limited as treatment itself is still in relative infancy. Interest in medication adherence in the last two years has blossomed but practice has not yet evolved to routinely include adherence assessment and interventions. Interventions are under study while clinicians and behaviorists learn to appreciate each other's strengths. Williams (1997) asserts "that it is the noncompliance of the providers that is reflected in our failure to implement adherence interventions that have been demonstrated to be effective." The study of adherence in antiretroviral therapy is still in the fact-finding stage. There have been few formalized research projects published to date. Surveys have been conducted in an effort to identify what is unique about adherence to HIV therapies. These mostly search for answers to why people don't take life-saving medications religiously. This section will not reiterate issues already presented but will specifically review the efforts to characterize the problem of non-adherence to antiretroviral therapy and the ongoing efforts to address the issues.

Documentation of Medication Non-adherence in HIV Disease

Given the impact of adherence on HIV care, many recent studies to characterize the prevalence of the HIV adherence problem have been conducted. HIV, like other chronic manageable diseases shares similar rates of non-adherence. A number of adherence patient surveys were conducted during 1998 and many of these were presented at the Twelfth World AIDS Conference, Geneva Switzerland. Some of these are summarized in Table 4.

Table 4: Surveys of Patient Adherence to Antiretroviral Therapies

Study	N	% of Patients with Incidence of Non-Adherence Within the Last Month	Findings
Chesney (# 281)	665	>43%	26% missed a dose the day before. 43% missed a dose in the past week.
Gallant and Block (1998)	359	43%	25% admit to non-adherence to the regimen on the preceding day.
Johnston (# 32389)	198	56%	31% had chosen not to take all drugs in the regimen and 41% took the medications irregularly
Jiminez-Nacher et al. (#32350)	135	22%	56% of patients took >80% of prescribed pills
Nakashima (# 393/32326)	1200	35%	9% indicated they rarely or never took their medications
Williams et al. (# 32374)	103	46%	54% took > 97% of their medications
Walsh et al. (#12298)	114	59%	Only 25% of patients admitted <80% adherence

The individual and public health costs, which are incurred as a result of insufficient pill adherence, have not been calculated. However, the development of resistance to an individual medication and the subsequent elimination of other medications in the same class through cross-resistance have been documented (Condra, 1995, Molla 1996). The individual consequences of insufficient pill adherence are inadequate control of viral replication. Drug failure can lead to accelerated progression of HIV illness and increased mortality. The public health consequences may result in an epidemic of resistant HIV strains. Numerous cases of the transmission of resistant strains of HIV have already been reported in the literature (Erice and Mayers, 1993, Imrie et al, 1997, Quigg, 1997) and the full implications of this have not yet been realized.

Reasons for Non-Adherence to Antiretroviral Therapy

In an attempt to better understand the problem of non-adherence to HIV medications a number of surveys have been conducted. The AIDS Clinical Trials Group (ACTG) conducted the first of these surveys and reported the results at the ICAAC meetings in 1997. Seventy six patients enrolled in clinical trials across the country given a standardized survey which included questions on why patients were missing their medication. The results are shown in Table 5.

Table 5: Reasons for Missing Doses of Antiretroviral Therapy (Chesney, 1997)

Reasons for Missing Doses	Proportion
Simply Forgot	40%
Slept through the dose	37%
Away from home	34%
Change in routine	27%
Busy with other things	22%
Too sick	13%
Depressed	9%

The survey also revealed characteristics of adherent versus non-adherent patients and found that non-adherent patients were:

- more likely to be working
- younger age
- depressed
- feeling stressed
- had pessimism about HIV disease
- lower levels of coping efficacy.
- more likely to consume greater quantities of alcohol (17 drinks per month versus 9 drinks per month)

Abstract Review from the Twelfth World AIDS Conference, Geneva Switzerland, 1998

The field of adherence to HIV therapies is still in its infancy. However, paced by the rapid development of HIV therapeutics over the past few years interest in HIV adherence has escalated. There has been little published research at this point however, the Twelfth

World Conference on AIDS represented the surge in interest with the submission of 146 abstracts with a main focus of adherence. In addition, adherence was mentioned as a key word in another 50 abstracts presented in Geneva. Table 6 represents a summary of abstract characteristics presented in Geneva. Table 7 shows abstract subjects grouped by category. Table 8 highlights the central issues and findings from Geneva and Appendix I summarizes all abstracts on adherence.

Table 6: Summary of Geneva Abstracts

Subjects	Total
Abstracts	130
Categories	8
Countries submitting research on adherence	18
Number of different investigators	122
Total participant studied	23,790
Mean adherence	54%

Table 7: Twelfth World AIDS Conference, Geneva, Switzerland. Abstracts by Category:

Adherence Categories	Table Abbreviation	Number of Abstracts Addressing Topic
General Adherence Overview	G	2
Characteristics of non-adherent patients and/or incidence or prevalence of non-adherence	C/P	35
Interventions/Strategies	I	54
Factors/Barriers	F	49
Adherence Assessment	A	11
Consequences	CQ	4
Adherence Theory	T	4
Costs of Non-Adherence	\$\$	1

Table 8: Central Issues and Findings that Emerged from the Research Presented at The Twelfth World AIDS Conference, Geneva Switzerland.

Reasons for Medication Non-Adherence

#1 forgot
 #2 and # 3 side effects and fatigue
 Difficulty concentrating

Determinants of Adherence

Participation in a clinical trial
 Belief that the medication is working
 Good social functioning
 Perceived professional support
 Older patients

Determinants of Non-Adherence

Youth
 Changes in routine
 Being away from home
 The mid-day dose and weekend doses are most likely to be forgotten
 Changes in routine contribute to non-adherence
 More complex regimens
 Regimens that require dietary restrictions
 Longer duration of therapy
 Side effects
 Living alone
 Alcohol and drug use may decrease adherence (not consistent)
 Demographics do not predict non- adherence, although two studies found that adherence was higher in men than in women
 Poor relationships with providers
 Regimens that are intrusive and disrupt normal activities
 Patients who are non-adherent the day before seeing their provider are 9 times more likely to have been non-adherent during the previous month

Interventions

Adherence is improved with family /friend / significant other support
 Increased supervision
 Early management of side effects

Evaluation of Adherence

Self reports of adherence are inaccurate
 The combination of pill counts and prescription refills can be more useful assessment tools if used in combination with indirect measures such as adherence questionnaires

BEHAVIORAL MODELS TO GUIDE THE PRACTICE OF THE MEDICATION MANAGER

Models designed to understand and predict human behavior are rooted in psychological theory. They attempt to provide a conceptual framework to guide the interactions or practice with individuals. No single theoretical model of behavior fully fits or explains the actions of people afflicted by a chronic disease. However, although a single model does not fully frame the challenges of adherence to HIV therapies, insight gained from several models can be illuminating. In reading a review of various theoretical models one may note the overlap in each of the models, none seeming perfectly discrete from another. This is in fact a reality as they have each been built on concepts identified in previous models.

The Health Belief Model:

The Health Belief Model, developed in the 1950s by a group of social psychologists at the US Public Health Service, was one of the earliest conceptual frameworks for understanding why individuals did, or did not, practice a variety of health and medical recommendations. (Rosenstock, 1974). Although it was originally designed to understand prevention behaviors, it has evolved to include other time points in health decision making such as screening, following medication regimens, keeping clinic appointments and other health-related behavior. It is presented here because of its concepts and role in the foundation of future models and not necessarily for its practical applicability to behavior change.

The health belief model was developed out of the social-psychological theory that encompasses value-expectancy in which, behavior is predicated from the value of an outcome to an individual and from that individual's expectation that a given action will result in that outcome (Becker, 1976). The premise of the health belief model is that an individual's readiness to take action depends primarily on two variables: 1. The perceived likelihood of being affected by an illness and how seriously it will affect him; 2. The individual's perception of the value of the proposed health behavior. If these assumptions are correct then behavior would be based on the desire to avoid or improve illness and the belief that a specific action would prevent or improve illness. In other words, what an individual believes about his illness and its particular treatment has a strong influence on the likelihood of adhering to that treatment. In the health belief model there are four elements, which in their aggregate, explain health-related decision-making. These elements include: (1) perception of the level of susceptibility (risk), this element is necessary but by no means sufficient, requiring element (2) for action; (2) perception of the degree of severity of the illness (consequences of contracting it or of leaving it untreated); (3) perception of the health action's potential benefits (feasible and efficacious); and (4) benefits versus the barriers of the treatment or therapeutic behavior (negative aspects include physical, psychosocial, financial, inconvenience, side effects). Rosenstock viewed the perception of susceptibility and severity as the impetus to act and the perception of benefits and barriers as the path of action. He also asserted that health decisions need a stimulus or cue to trigger the whole decision making process. This "cue to action" signals consciousness and can be internally driven, by e.g. symptoms or externally driven, e.g., by doctor's office reminder cards or media information. The health belief model also recognizes the influence of other

diverse variables that might influence a patient's perception and therefore influence decisions.

The correlation of the four elements and adherent behavior has been the subject of numerous research projects in the past 25 years. In a review of 46 studies of the Health Belief Model, including 29 published since 1974, Janz and Becker use a significance ratio to characterize the influence of Health Belief Model elements on health decisions. The significance ratio was determined by dividing the number of positive, statistically significant findings for each Health Belief variable by the total number of studies reporting significance levels for that variable. In their review, studies were classified by behaviors found at various phases of health and illness. These include preventive health behaviors; illness behaviors, sick-role behaviors or clinic utilization behaviors.

Across the three classes of studies reviewed perceived barriers to adherence clearly emerged as the strongest dimension of the Health Belief Model, transcending all phases of health and illness, and providing valuable practical information for the development of an adherence intervention. Although still significant, perceived susceptibility had a weaker correlation to sick role behavior than the other dimensions and the threat of a severe illness was not found to be a strong motivator for preventive behavior. Table 9 describes the phases of illness and health studied under the health belief model. Table 10 shows summary significance ratios for sick role, preventive role and clinic utilization behaviors, as well as significance ratios for sick-role and preventive behaviors alone from the Janz and Becker review for studies published after 1974.

Table 9: Phases of Illness and Health Studied under the Health Belief Model

Phase of Illness or Health	Description
Preventive health behavior	
Clinic Behavior	
Sick-role behavior (includes diabetes, hypertension, endstage renal disease)	The diagnosis has already occurred.
Illness behavior	Readiness to seek medical help and health care utilization
Chronic Illness behavior	Applies to those in whom the incomplete resumption of usual roles, residual disability, irreversible pathology, and possibility of stigma is likely to occur.
At risk health behaviors	Requires sick role behavior from a person who does not feel sick. Has the duties of illness behavior but not the privileges, such as reduced social obligations attached to this state.

Table 10: Significance Ratios for Sick-Role Behaviors, Preventive Behaviors, And Sick-Role/Preventative/And Clinic Utilization Behaviors

	Susceptibility	Severity	Benefits	Barriers
Sick-role behaviors	73%	85%	75%	91%
Preventative Behaviors	83%	36%	82%	100%
Sick role, preventive role, and clinic utilization behaviors	81%	65%	78%	89%

The health belief model has been criticized in its inability to uniformly correlate beliefs with actions. Although many studies have documented significance to beliefs and behavior, the literature is laced with contradictory conclusions concerning the relationship. For example, Kirscht and Rosenstock cited significant relationships between perceived susceptibility and adherence to an antihypertensive regimen while three nursing studies

found no significant correlation between health belief elements and compliance to hypertensive regimens (Redeker, 1988).

Some of the health belief criticism stems from the fact that too much of health belief research has been retrospective. Another criticism stems from the use of diverse and inconsistently reliable scales to measure relationship (Redeker, 1988). In particular, it has been noted that beliefs that precede treatment versus beliefs during treatment do not correlate with adherence. This spurns the question of whether health beliefs cause compliance or whether compliant behavior causes people to adapt certain beliefs. (Becker et al., 1979). It could be interpreted that beliefs may be a necessary, but not always sufficient, variable in behavior change.

However, there is enough evidence that assessment of health beliefs can guide interventions aimed at improving adherence. By knowing which elements are below a level necessary for adherence, the provider may be able to tailor an intervention to suit the needs of that patient. In spite of contradictory evidence, it would seem that not knowing a patient's beliefs represents a handicap in creating an effective intervention.

Phases of health and illness that have been studied in the health belief model are described in table 9. Different phases of health and illness have been studied separately because there are different determinants needed to understand them. In attempting to understand HIV in the context of the health belief model one is struck by the lack of a perfect fit. HIV is a chronic disease yet often, at this point in the epidemic, without symptoms to trigger health behaviors or to seek treatment. Perhaps a combination of "chronic disease" with "at risk". analysis is best suited to individuals with asymptomatic HIV. To use the analysis of Kasl (1974) in his review of the health belief model and behavior related to chronic illness:

having asymptomatic HIV requires sick role behavior from a person who does not feel sick, requires medication even though there is no change in health status and requires treatment for an indefinite period of time. That situates people with HIV in a somewhat unique position in our understanding of health beliefs and behavior.

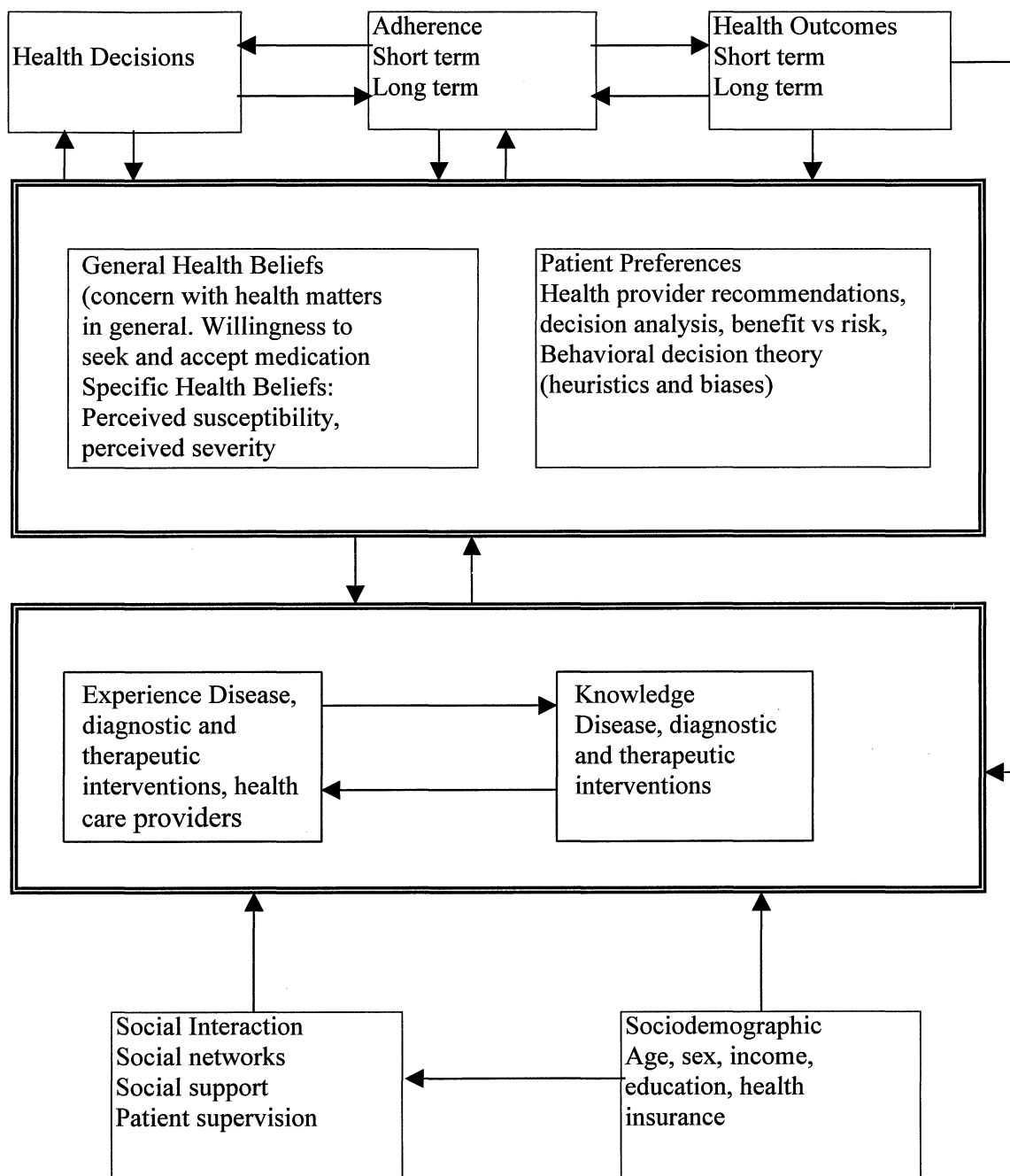
The utility of a practical application of the health belief model is demonstrated by Green et al. (1979) who used the findings of a survey of beliefs of outpatients with primary hypertension to develop an intervention to improve health related actions. The survey found that 70% of patients reported a lack of family support and understanding about their health. Green then compared three interventions in 400 patients: an exit interview to educate patients about their medications, a home visit to increase family support, and a small group discussion to empower patients. The educational interview and the family support intervention at home were found to be the most effective strategy to improve medication adherence. The home visit alone achieved almost the same improvement in adherence (Levine, 1979) as the two together.

The Health Decision Model:

The health decision model, developed by Becker during the 1980s, was an effort to build on the health belief model and improve it (Eraker et al., 1984). It incorporates theories of decision analysis and behavioral decision theory to develop a model of health decisions and resultant behavior. Decision analysis provides a means for patients to express their preferences about critical trade offs between benefit, risk, and sometimes about quantity and quality of life. Behavioral decision theory identifies a number of general inferential rules that patients use to reduce difficult mental tasks to simpler ones. The health decision model

also recognizes the contributions of such factors as cultural beliefs, parent's beliefs, previous experience with illness, and information/misinformation given to them by non-medical sources. One will notice that in the health decision model the elements of the health belief model are framed differently for example benefits and barriers (risks) fall into the category of patient preferences. The health decision model incorporates findings of years of research on barriers or factors that influence adherence, including the brevity of the encounters with their provider and general satisfaction with their health care. In the Becker model, a patient is more likely to adhere to medication regimens when he believes the provider is correct, the illness can cause harm, and that the prescribed therapy will reduce the complication or death, or his health will improve (Becker, 1979). Figure 1 demonstrates the elements of the health decision model.

Figure 1. The health decision model (Eraker et al.1984, p261)



Behavior Modification:

The term behavior modification is often associated with brain washing conditioning techniques. We are reminded of Pavlov's dogs and Skinner's pigeons. However, behavior modification is a collaborative effort, that recognizes that an individual's behavior is influenced by its antecedents (external and internal events that trigger or elicit a behavior) and consequences. Antecedents for example may include the sight of food for an individual with a weight problem. An antecedent for not following a medication regimen may include a sense of hopelessness about one's illness. Behavior modification involves identifying behaviors that need to be changed and identifying when they do and do not occur. In addition, assessing, monitoring, and manipulating the impact of antecedent and consequent events are also necessary in changing behavior. Some techniques employed in behavior modification include:

Self monitoring:

One way that patients can be enlisted as collaborators in their health care is by teaching them to self-monitor. Self-monitoring is a means of raising one's consciousness and is based on the premise that behavior change is unlikely to occur in the absence of an awareness of the behavior.

Dunbar and Agras (1980) summarized guidelines, which can be used to increase medication adherence using a behavior modification approach:

- 1 Ask the patient to self-monitor, by observing behaviors that have a positive outcome
- 2 Use easy to use records
- 3 Ask the patient to assess readily observable behaviors
- 4 train the patient in self monitoring
- 5 Reinforce the patient's accuracy in recording rather than any improvements or changes in regimen related behavior

- 6 Let patients know that their records will be checked for accuracy
- 7 Ask patients to record at the time the behavior occurs rather than at the end of the day or the end of the week.

These guidelines were later supplemented by Friedman and Litt (1986)

- 1 Provide immediate feedback and encouragement to the patient about self-monitoring.
- 2 Patients should eventually record behavior before rather than after it occurs
- 3 It is better to monitor a behavior than a goal.

Goal setting:

Goal setting is widely used in behavioral modification approaches. Again, the patient is the key player in setting goals and working collaboratively in order to increase the likelihood of their participation. Goals should be realistic and whenever possible people close to the patient should be involved. (Meichenbaum, 1987). Goals should be moderately specific but not overwhelming. In addition, goals should lead to meaningful rewards that can be offered as soon after the positive behavior as possible. Goals have been described as homework assignments and divided by devising the assignment, presenting the assignment, and monitoring the assignment. (Martin and Washington). Following principles used in behavior modification, greater adherence to tasks will be achieved if the patient helps define the assignment. The health care provider can further enhance compliance by having the patient imagine ways in which the goals might not get completed.

It has been suggested that the provider might even have the patient practice the assignment in their office, but there is little doubt that this would be more effective if practiced in a supervised fashion in the patient's home environment. Success of goal completion must be then attributed to the patient's efforts and not a therapeutic technique (Meichenbaum, 1987).

Failure to achieve goals must be explored and even assessed in a health belief framework of understanding the patient's perception of the task.

Corrective feedback:

Corrective feedback alone is not sufficient, but it is helpful when combined with self-monitoring and goal setting relative to the patients ability to adhere to treatment regimens. Feedback should be accompanied by encouragement and perhaps additional training if necessary.

Behavioral contracting

Behavioral contracting is a negotiated agreement between the patient and the health care provider that combines goal setting with reinforcement and is conditional on achieving the goal. It is an integral component of the behavior modification process that actively involves the patient in the decision making process. Central to the contracting process is the identification of specific behaviors and how they might be carried out. Advocates of behavior modification techniques suggest that behavior modification (medication adherence) will be most successful and most durable when the patient actually suggests the specific interventions that are to be undertaken. In order to accomplish this, however, the health care worker must lay the groundwork by asking questions to engage the patient in the solution. This can be accomplished by exploring with the patient those situations in which he has not been able to adhere and identifying what is different about these situations. Alternatively, the patient can be given options from which to choose, which also serves to increase the patient's sense of personal control.

Unfortunately, evidence suggests that behavioral contracting may be effective only while it is being monitored (Cummings et al., 1981), thus the provider should expect a long-term relationship or a short-lived success. Other predictors of failure of behavioral contracts include imposing contracts that are not negotiated with the patient, not specifying provider

responsibilities and not using reinforcements.

Commitment enhancement:

Several measures have been proposed that are likely to enhance commitment to medication adherence (Meichenbaum, 1987):

- 1 Encourage patients to tell people about their commitment
- 2 Encourage specificity concerning the commitment, i.e. frequency, duration etc.
- 3 Solicit a commitment in oral and written forms.
- 4 Involve the patient in the choice of intervention.
- 5 Encourage patients to self-monitor their behavior
- 6 Positive behavior must be attributed to the patient.

Reinforcement:

Health related behaviors can be influenced by rewards and negative consequences. Rewards can take the form of praise, public acknowledgement or even food vouchers, movie tickets, or lottery tickets. Negative consequences range from the removal of positive reinforcement to the implementation of a deposit system, where patients are required to make a financial deposit which is refunded for adherent behavior. Self-reinforcement is a third and perhaps more palatable measure to some than either rewards or negative consequences. Self-reinforcement may include having patients keep a flow chart of their progress or in HIV care using critical laboratory values such as viral load. Again, inherent in self-reinforcement is the notion of the patient owning their success. Some have involved family or friends in the reinforcement process for the provision of feedback as well as to integrate the behavior into their normal lifestyle.

The Strengths Model:

During the case management years of the 1980s, the strengths model was developed by Chamberlain and Rapp (Rapp, 1998) to help people with mental illness achieve goals that

they set for themselves. The principles that serve as the underpinnings of the strengths model are not only germane to those working with people with HIV, but can serve as a sound basis for supporting adherence.

In the strengths model, case management services are tailored to the unique needs of each person. Work is done and decisions are made *with* people, in a partnership, not to people, while recognizing that all individuals are interdependent.

Principles of the Strengths Model (Rapp, 1998):

1. The focus is on individual strengths rather than pathology.

Focus on what the client has achieved so far, what resources are currently available to the client. This allows for a different way of thinking about clients that recognizes their own power to take care of themselves. It honors their skills, competencies and talents as opposed to their deficits.

2. The community is viewed as an oasis of resources.

This principle speaks to the importance of the client's environment. Each individual's community is unique and must be assessed and utilized as a source of strength for that individual. The model supports the use of "naturally occurring resources, thereby counting not only on the strengths of the individual but the strengths of those around them. The case manager's role under this principle is to be a catalyst for involving others in the client's life, that is to create collaborators.

3. Interventions are based on client self-determination.

Clients have the right to determine the form, the direction and substance of the case management help. Case managers should do nothing without the client's approval,

involving clients in all decisions. It is the case manager's role under this principle to assess strengths and work on behalf of the client to achieve the client's goals. In understanding why a client does not take their medication, for example, Rapp asserts that it is the only way for them to express their opinion and exert their sense of power.

It sometimes requires the blending of strengths or guiding the client to recognize their own strengths. The creation of new possibilities for the client is a contrast to talking them into something. Reasonable and safe choices need to be presented so that the client can develop the confidence of self-determination.

4. The case manager-client relationship is primary and essential.

Rapp describes the case manager-client relationship as the anchor during rough and anxious times. It is the safety of the relationship that supports the client to cope with the demands of change, new information, the environment and other people. "The client needs a traveling companion, not a travel agent (Rapp, 1998)," stressing the cooperative nature of the client-case management relationship.

5. Aggressive outreach is the preferred mode of intervention.

Outreach into the client's own environment offers fertile ground for assessment and intervention. Office and telephone contact limits the information received to what the client says in an artificial setting. Training skills inside a clinic or agency does not necessarily transfer to the home setting. Amid the distractions of the home, skills that seemed well integrated may be forgotten. The case manager can also use home visits to provide direction to clients, model behaviors and to teach others. The identification of resources may also be done best in the home environment.

6. People suffering from major mental illness can continue to learn, grow, and change.

This aspect of the strengths model recognizes that the affliction is only one aspect of the individual. “They, like us have a history of pain as well as accomplishment, of talents and foibles, of dreams and aspirations.” A central tenant of the model is the belief in individuals’ capacity to better their lives. The notion of “can do” must permeate the process and relationships.

In summary, the roles of the case manager in the strengths model are: Engagement and relationship, strengths assessment, personal planning, resource acquisition, and collective, continuous collaboration and gradual disengagement.

The strengths model, although developed in the mental health community, is generally founded on principles that strive to change behavior and improve lives. The principles that have been used to empower individuals with mental illness transcend this population and can be generalized for other purposes.

The Transtheoretical Model of Change:

The Transtheoretical Model of Change, developed by Prochaska (1983), is based on an understanding that behavior change occurs in stages over time and that interventions cannot be successful unless the desire to change is internally driven and accepted. During the process of change cognition and affect evolve. This theory has been applied successfully to addiction behavior change, diet and weight control, exercise, screening and smoking cessation. The focus of this model is motivational readiness or intention to modify problem behaviors. Prochaska describes five stages of change through which individuals progress in

the process of modifying their behavior: precontemplation, contemplation, preparation, action and maintenance. Although these states represent a continuum, movement through these states is not unidirectional. In fact, the model is based on the inevitability that individuals move back and forth, with relapse as an expected part of the process. Each Stage of Change is characterized by conscious and unconscious thought processes and strategies. Ten such processes of change have been identified which are thought to mediate the transition to each stage. The association of stages, their processes, and appropriate interactions are shown in Table 11.

Proponents of the model acknowledge the influence of pros and cons of change throughout the process, noting that across studies, the pros are a stronger influence of change than the cons. Prochaska viewed the pros as facilitators of change while the cons are seen as barriers to change (Prochaska et al., 1994).

Another important characteristic of this model, no doubt evolved from its predecessors, is the emphasis on self-efficacy. Prochaska cites Banduras' (1982) definition of self-efficacy as a mediator between knowledge and action. In the transtheoretical model of change, self-efficacy is felt to provide confidence to change. Confidence and temptation are in a delicate balance across all stages of change.

The stages of change and their processes can guide the provider with appropriate guidance based on the patient's stage of readiness and can prepare the astute practitioner for the inevitability of relapse.

Table 11: The Transtheoretical Model of Change

Stage	Processes	Definition	Reasons	Behavior	Intervention/interaction
Precontemplation	Consciousness raising Dramatic relief Environmental Reevaluation	not considering in the next 6 months	Uninformed or underinformed about consequences. Demoralized about ability to change, Lack confidence	Defensive, Resistant Low confidence, high temptation	Help raise consciousness and re-evaluation, access accuracy of information. Increase awareness and understanding of self image
Contemplation	Self-reevaluation	Seriously thinking about change in the next 6 months	Still ambivalent about barriers	Open to feedback, evaluating how to make change More confidence and less temptation	Review pros and cons of behavior change. Question about re-evaluation.
Preparation	Self liberation	Ready for action. Planning change in the month		Taking steps toward action, trying it on. Self-efficacy building. More confidence and less temptation	Identify social support in family, friends, groups. Help prepare for change, provide feedback about successful behavior changes in patients past. Begin to teach techniques.
Action	Counter-conditioning helping relationships Reinforcement management Stimulus control	Overt modification of the behavior for some period of time	Confidence as increased sharply but temptation has decreased more slowly	Relapse likely Self-efficacy building. Situational temptation = cues for relapse	Reinforce small steps, provide alternatives, Relapse prevention. View relapse as a learning experience. Identify contingency plan.
Maintenance		Begins 6 months after continuous successful behavior change		Self-efficacy plateaus	Continue awareness of relapse risk

The Locus of Control Model:

The locus of control theory reflects the belief that the extent to which a person perceives his ability to change or control his life impacts his willingness or ability to comply with medical treatment. In this behavioral construct individuals are viewed as internally oriented or externally oriented. Those who are internally oriented are believed to be self-oriented and those who are externally oriented are influenced by others, the system or fate. Simple statements like “the doctor says I have” versus “I have a certain problem” reflect internally versus externally oriented differences. There is evidence that internally oriented individuals may be less likely to smoke (Eiser et al., 1989) and more likely to have had a recent pap smear (Bundek et al., 1993) or breast exam (Redeker, 1989). Furthermore, given an external viewpoint, medication adherence is less likely. Those who are externally based believe they have less control over their environment.

Individuals of low socioeconomic status or members of minority groups are more likely to exhibit external locus of control behavior. Therefore it is relevant medication adherence in individuals with HIV infection, a disease which is known to be over-represented in poor and minority communities. “Continuous insults to personal integrity and dignity can predispose individuals to attitudes of helplessness or fatalistic behaviors” (Hussey, 1989).

Locus of control is influenced by psychosocial factors (Hussey, 1989):

- 1) Cultural-fatalism (feeling ostracized by society)
- 2) Lower socioeconomic status
- 3) Minority status
- 4) Familial reinforcement(a child who continuously experiences disapproval or whose wishes are chronically ignored learns that he cannot control his environment or what happens to him).

Alternatively, factors that are associated with a positive locus of control include ego-identity, self-worth, confidence, self-esteem and self-acceptance. Individuals who are adherent to treatment regimens are often described as motivated. The degree of “motivation” exhibited by an individual may be a reflection of their locus of control beliefs. Motivation is manifested by action in situations that are meaningful to an individual and are influenced by social and cognitive factors as well as a sense of self-preservation. The role of self-efficacy, in locus of control, is a relevant concept that links an individual's feelings or thoughts about his own capability of accomplishing any given task to his actual ability to achieve the goal (Bandura, 1981). Furthermore, if an individual believes that he cannot achieve a goal, he is less likely to try. Alternatively, Bandura maintains that individuals with stronger self-efficacy will exert a more active and persistent effort. In a study designed to improve self-efficacy and self-esteem, Frank et al.(1995) demonstrated an 85% adherence rate and only a 10% drop out rate in a 3-year study of compliance in older adults.

Buchmann (1997) suggested in “Adherence: a matter of self-efficacy and power” that professionals can foster self-esteem by dividing recommendations into incremental steps that can be mastered at a pace comfortable for the patient. Perhaps, compartmentalizing the treatment experience at a controlled pace, individuals unaccustomed to experiencing power and self-determination can have a successful treatment experience.

The Information, Motivation, and Behavior Model (IMB):

The IMB model, developed by Fisher and Fisher may be described as a second generation model. Like to the transtheoretical model, it is built on its predecessors and is very outcomes based. The model was born after a thorough review of AIDS risk reduction literature revealed that interventions that stressed information, motivation and behavioral skills were more successful than those that did not. The review also led the creators to the conclusion that the variables of information, motivation and behavior were the most sound bases for intervention (Fisher and Fisher, 1992). Hence, they developed an AIDS risk reduction model based on three determinants: Information, motivation and behavior where information and motivation were felt to be the triggers for behavioral change and maintenance. Fisher and Fisher point out that information is a necessary but not sufficient variable to behavior change and that an individual must also be motivated to effect a change. This is substantiated by data that reveals that attitudes consistently predict their practices (Fisher and Fisher, 1992). In the IMB model health beliefs are believed to be determinants of motivation however the Fishers argue that other health belief variables, such as susceptibility and severity are inconsistently correlated with risk reduction.

Fisher and Fisher are currently developing an adaptation of the IMB model for medication adherence which is summarized in Figure 2, with additions from Andrews in italics. This proposed model may represent the most comprehensive understanding of adherent behavior thus far. IMB reflects findings of HIV surveys, which identify barriers to adherence as well as relevant characteristics of previous models, which can be generalized to medication adherence. Constructs of the model demonstrate the relationship of adherence information and adherence motivation to adherence behavioral skills which are shown in relationship to actual adherence behavior and to medical outcomes. As this is a work in progress, little has been said about context characteristics, which currently appear as independent variables.

Italicized entries represent Andrews' modifications

Figure 2: Preliminary Adaptation of IMB Model to Adherence (Fisher and Fisher, 1998)

Italicized entries represent Andrews' modifications

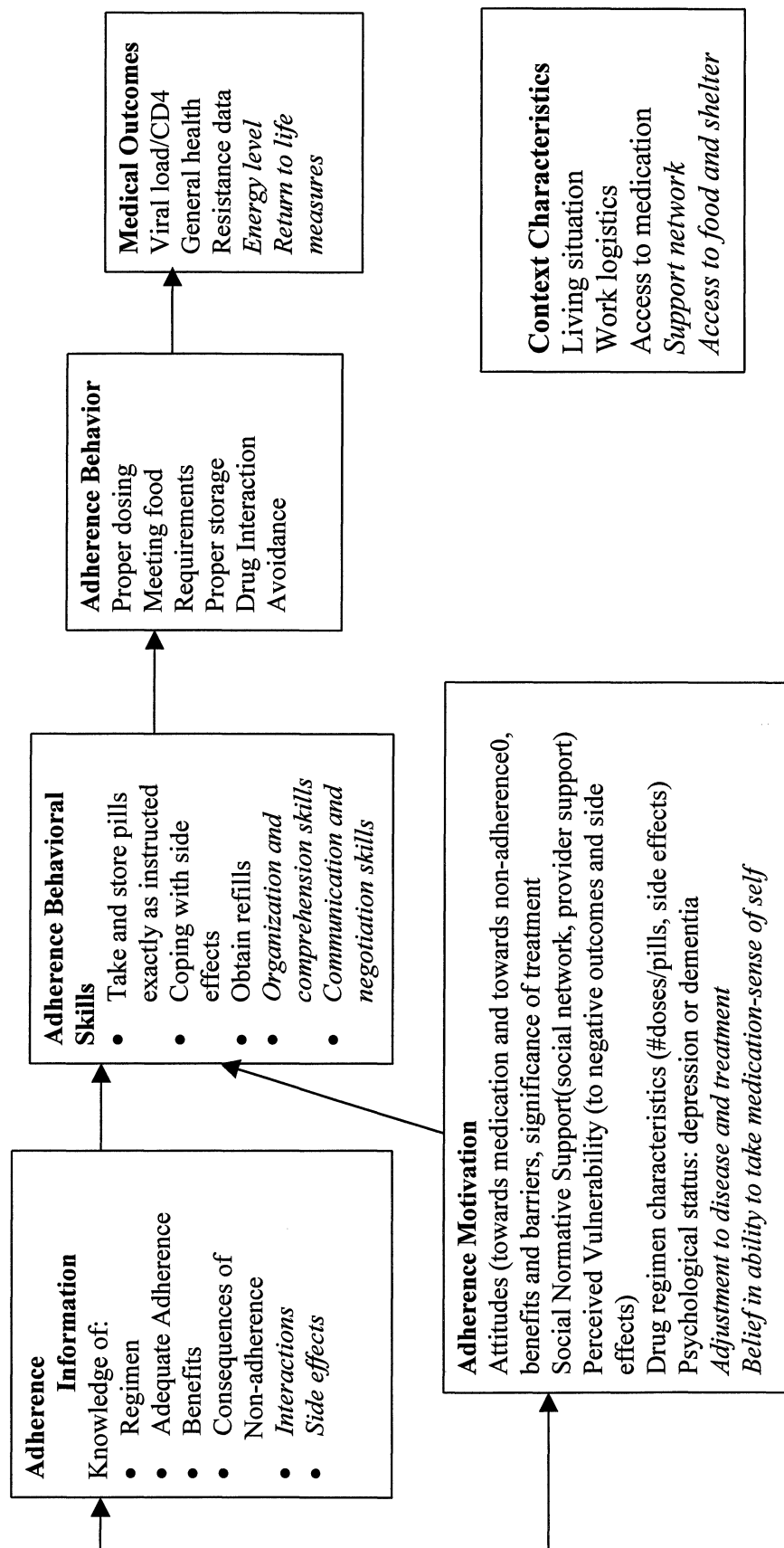


Table 12: Relevant Principles of Seven Behavioral Models in the Practice of**Improving HIV Adherence:**

Model	Relevant Principles
Health Belief Model	<p>Identify: patients perceptions of illness and treatment, barriers including fear of failure, sense of I can't do it, I can't afford it, I am not good enough</p> <p>Periodically ask patients "do you think this is working"</p> <p>Expect barriers and work together on getting through them</p>
Health Behavior	<p>Modify interventions to reflect patient preferences. Assess patient's perceptions of the benefits versus the risks</p> <p>Learn about the patient's cultural beliefs</p>
Behavior Mod	<p>Approach medication as a collaborative project with the patient as a key</p> <p>Learn values and beliefs</p> <p>Learn what behaviors need to be changed</p> <p>Identify antecedents for non-adherent behavior</p> <p>Identify vulnerable times for non-adherent behavior- when non-adherent behavior does and does not occur</p> <p>Have the patient develop his own plan for achieving adherence</p> <p>Have patient set their own goals – involve loved ones in the patient's commitment to adherence</p> <p>Have patient imagine ways that the goal might not be accomplished</p> <p>Practice organizing medications and following a schedule, in the home setting amidst normal distractions</p> <p>Reward with immediate feedback, like timely enthusiastic reports of viral load</p> <p>It is better to monitor a behavior than a goal</p> <p>Teach self-monitoring if appropriate.</p> <p>Engage patient in discussion to identify situations in which they don't adhere</p> <p>Attribute positive adherent behavior to the patient, not the intervention</p> <p>Become the patient's cheerleader and work as a team to lower viral load</p> <p>Reinforce positive adherence behavior-reward for X number of undetectable viral loads (food vouchers, movie tickets, lottery tickets)</p>
Strengths Model	<p>Work in partnership with the patient</p> <p>Focus on individual strengths and achievements, not pathology</p> <p>Honor skills and competencies and talents, not deficits</p> <p>Identify collaborators</p> <p>Use visits to the home for assessment, intervention, modeling behavior, identifying resources, teach family/friends about patient's treatment and the importance of adherence</p> <p>Utilize community agencies for support</p> <p>Exude a "can-do attitude"</p> <p>Foster self-efficacy and power</p>

Model	Relevant Principles
Locus of Control	<p>Recognition of locus of control may influence how providers conceptualize patient's response to treatment</p> <p>Assess the patient's beliefs in themselves and in their ability to achieve adherence to medication regimen</p> <p>Work with the patient to identify ways in which they already have control over their behaviors and life (Taking care of children, getting to appointments)</p> <p>Identify who in the patient's family or extended family and friends is most supportive</p> <p>Support self-efficacy</p>
Transtheoretical Model of Change	<p>Assess the stage of readiness</p> <p>Tailor the intervention/interaction to the stage of readiness</p> <p>Proceed cautiously at earlier stages</p> <p>Review the pros and cons of treatment and adherence</p> <p>Pros are a stronger influence than cons so frame adherence message as a positive message, like eroticizing safer sex</p> <p>Self-efficacy provides confidence to change. Build patients confidence at every opportunity</p> <p>Identify social support for change</p> <p>Be aware of the ongoing and delicate balance of confidence versus temptation. It looms until the final stages</p> <p>Relapse is inevitable, be aware of the possibility particularly at certain time points, have a relapse plan</p>
Information Motivation/ Behavior	<p>Information and motivation are triggers for becoming adherent and staying adherent</p> <p>Information, motivation, and behavioral skills are all necessary for adherence</p> <p>Skills should be taught, rehearsed, and refined in a script-like fashion</p> <p>Role-playing can help to evaluate and improve skills</p>

THE MEDICATION MANAGER

A Precedent for the Medication Manager: The Case Manager

The field of case management flourished in the mental health community during the 1970s when deinstitutionalization forced large numbers of people with mental illness out of structured environments into community based settings. The goal of deinstitutionalization was to stabilize clients with as few restrictions as possible. Economic pressure and the development of psychotropic medication propelled the movement faster than services could be established (Segal and Aviram, 1978). Clients were left to negotiate the maze of services in the community (Schwartz, Goldman, and Churgin, 1982). Delivery of services became even more complex with the development of separate and fragmented programs. Those most in need of services began to suffer at the hands of the evolving system. The Community Support Program of the National Institute of Mental Health was the prototype for the provision of case management and supportive services in the early development of these programs (Test and Stein, 1980). It provided the generic framework on which case management models have been built (Bond et al., 1988). The issues of the mentally ill were addressed by creating a case management system which encompassed two central features: 1) provision of individualized advice, counseling, and therapy to clients in the community and 2) linking clients to needed services and supports in community agencies and informal helping networks (Rothman, 1992). In 1974 the Child Abuse Prevention and Treatment Act provided for case management in programs focused on abused children. In the 1980s Dunst and Trivette proposed a case management model aimed at enabling clients to solve problems, meet needs or achieve aspirations by promoting acquisition of

skills that support and strengthen functioning to permit greater sense of individual or group control (Dunst and Trivette, 1989).

Through the years the practice of case management has become incorporated into a variety of fields including child welfare, community based long term care, severely emotionally disturbed children and adolescents, substance abuse, disabled adults and elderly, homeless and individuals with HIV and AIDS.

There is considerable variation of case management service provision across these diverse populations. The backgrounds of case managers have been as varied as their roles, including social work, psychology, nursing, and vocational rehabilitation. More recently case managers working in the AIDS field have added even more diversity to the field. Individuals with no previous training or experience grew into case management positions, with a primary qualification of willingness to serve. Their enormous contributions to the epidemic and to the lives of individuals with HIV have opened the minds of even the most elite.

The roles of case managers in HIV care have included securing entitlements, arranging for wills and living wills, counseling on HIV disease and risk reduction, problem solving, finding food, housing and shelter for those who need it. Working through issues of childcare and custody with dying parents and arranging for medical care and medication coverage. Many of those serving in this field have performed their responsibilities with caring and commitment with very little training. The field of HIV case management has been a model for the next generation of health workers, the medication manager.

The Theoretical Basis for the Practice of Medication Management

Rationale: The concept of the medication manager is grounded in behavioral theory, the literature on adherence in chronic diseases and on the most recent research on adherence to antiretroviral therapy. Complex drug regimens are viewed as disruptive to normal daily routines and may require significant adjustments to lifestyle. Sometimes simple factors in the patient's routine prevent schedules from being followed. Understanding patient's beliefs about their illness and its treatment may shed valuable light on targeting interventions. Understanding a patient's worldview, their cultural beliefs, their perception of themselves, and their abilities can also guide efforts to improve adherence.

Many patients state their reason for non-adherence as simply forgetting. Patients who are successful in adhering to antiretroviral regimens state the need to develop a routine and to establish cues in the course of their day. Helping the patient to identify vulnerable times for non-adherence can be a proactive intervention. Organizing complex regimens around meals and other medications is a daunting task for even the most experienced pill taker. Many skills are necessary to organize and follow through on taking a three-drug regimen that requires dosing two or three times a day carefully scheduled around meals and other medications.

Data has been presented in this paper on the positive effects of increased support and supervision, the value of home visits and the benefits of tailoring regimens to a patient's lifestyle. It may greatly benefit the patient and their ability to adhere to identify a support person that can help keep them on track. However, the patient may not have a

willing or able individual to do this or may simply not be able to readily identify such a collaborator. As adherent behaviors form, timely feedback is valuable along with reinforcement of positive behavior. Helping the patient to identify their strengths rather than focusing on their weaknesses by acknowledging successes contributes to self-efficacy.

The role of the medication manager is to help the patient gain the skills necessary to adhere to their complicated regimens and to help the patient believe in their ability to carry out their goals. Early intervention to evaluate lifestyle as well as potential problems in maintaining medication schedules is supportive of adherent behavior. Ongoing feedback and problem solving may prevent the loss of adherence and the loss of a viable medication option. A liaison to provide timely feedback between the patient and provider can prevent the patient from feeling overwhelmed about problems in adherence.

The Referral to the Medication Manager:

In an era of limited resources the medication manager must be used as effectively as possible. Given a potential caseload of approximately 35-45 patients at a time it is important to identify those patients who will benefit most from the time and skills of the medication manager. One candidate for the services of the medication manager would be a patient who is highly motivated to be treated, believes that the medications will prevent morbidity and mortality from AIDS, understands the consequences of non-adherence, but does not necessarily have the skills to adhere to their regimen. Conversely, a patient who is not ready to accept treatment and its burdens would not likely benefit from interventions aimed at improving pill taking behavior. Thus, screening patients to

identify appropriate referrals is an important component of an adherence enhancement program.

The screening process must be realistic and not cumbersome yet effectively identify traits of patients who are likely to benefit from adherence services. Ideally, the screening will have a high degree of sensitivity, meaning that it will identify all those who need the service most and a reasonable degree of specificity, meaning that it will screen out those who are not ready for the service. During the screening process the medication manager will need to ascertain if the patient is non-adherent, if they value adherence, if they are ready to change their behavior and if they are at high risk for disease progression.

One obvious criterion for referral to a medication manager would be the presence of non-adherent behavior. Unfortunately, evaluating medication adherence has historically been and continues to be a complex and elusive problem. There are no perfect qualitative nor quantitative measures for evaluating adherence. Even if one could identify the presence of non-adherence the currently available techniques for assessing how non-adherent are quite imprecise. Methods of assessing adherence have included patient report, patient interview, counts of leftover pills and calculation of days between prescription refills. Each of these methods alone offers limited information on a patient's medication adherence behavior. Serum drug levels have also been obtained in an attempt to measure adherence but are generally best at approximating levels of drug taken during the previous week. Medication adherence has also been studied using special medication bottles that have been designed to record the time of a medication bottle opening. These Medication Event Monitoring Systems (MEMS) have been devised specifically to

observe pill-taking behaviors but can also be skewed by the simple act of opening the bottle.

The Morisky Medication Adherence Scale (1986) is a four-item scale that has demonstrated both concurrent and predictive validity with regard to antihypertensive regimens. More recently this scale has been studied as a screening tool for antiretroviral therapy adherence. The premise of the scale is that non-adherence is likely to take the form of forgetting, carelessness, stopping the drug when feeling better or starting the drug when feeling worse. The scale was designed to elicit “yes” answers which patients have a tendency to favor when speaking with their health care provider. The following questions are included in the scale:

- 1 Do you ever forget to take your medicine:
- 2 Are you careless at times about taking you medicine?
- 3 When you feel better do you sometimes stop taking your medicine?
- 4 Sometimes if you feel worse when you take the medicine, do you stop taking it?

Each yes is given a score of 0 and each no is given a score of 1. A score of 0-1 is considered a high score, 2-3 is considered a medium score and 3-4 is considered a high score.

When using the scale as a predictor for hypertension control Morisky found that 75% of the patients who scored high on the scale had their blood pressure under control at year 5, compared with 47% under control for those who scored low.

Given the importance of identifying those who need adherence enhancement services most a score of 2 can be used as a trigger for only moderate adherence and specific areas of deficit can be targeted for intervention.

Other measures of adherence can be employed at the screening process as part of a

multifactorial process. These should include a self report of adherence during the previous week and an assessment from the patient's provider.

A second important area of screening is the patient's readiness for adherence and intervention. This can be ascertained by applying a combination of patient beliefs with the transtheoretical model of change to the screening process. The interventions applied through the medication manager are intended to target those who are at least contemplating if not preparing for adhering to antiretroviral regimens. In the contemplation stage of change the medication manager may have limited impact on adherence behaviors. Patients who are referred in the preparation stage can benefit from a health professional who can identify strengths and past successes, begin to teach them adherence skills and help them identify support. Specific interactions in later stages are also identified in Table 11.

The patients preferences and goals must be included in an assessment by the medication manager. This impacts their motivation and readiness and should be specifically addressed in a screening interview.

Another factor in evaluating the appropriateness of a medication manager referral is risk for disease progression. This can be determined by viral activity, based on viral load and CD4 counts. Although adherence is no less important for those with low or undetectable viral loads these patients may choose to wait for treatment or choose simpler protease sparing regimens.

Logistics of the Medication Manger Practice:

The medication manager is a health professional who does not necessarily have a

nursing background or a pharmacy background. This individual will work closely with the provider and other members of the health care team to improve *adherence behaviors* and will not be responsible for prescribing or changing medication regimens in any way. Given the medication managers central role in orchestrating the adherence effort and the importance of working closely with other members of the health care team, the medication manager will ideally be located in an HIV clinic. This will afford maximal supervision and opportunities for this para-professional and will enhance communication and the multidisciplinary effort of the program. Supervision is an important feature of the medication manager program and would be appropriately administered by a clinic nurse or physician.

Funding the Medication Manager Program:

Funding of the medication manager program could come from three distinct sources. These include the state via the legislature, national funding via the Ryan White program, or privately via the pharmaceutical industry or private foundations. There is currently a proposal being developed to ask for funding from the state in this legislative session. A proposal has also been drafted to seek funding from the pharmaceutical industry. This option seems particularly viable in light of the benefits for drug companies who would gain from patients taking their medication. The following is a proposed budget outlining the costs of training, supervision, salary and benefits for 10 medication managers for the state of Connecticut.

Proposed Budget:

Item	Cost/MM	Number of Positions	Total
Medication manager (MM) salary, benefits, and overhead	\$50,000	10	\$500,000
Administrative overhead	\$7,500 (15%)	10	\$75,000
Program costs (brochures, pill boxes, etc.) per site	\$10,000	10	\$100,000
Medication manager Training Program	\$1,000/MM	10	\$10,000
Clinical Supervision	\$ 3,000/year/MM		\$30,000
Total			\$715,000

The Principles and Practice of the Medication Manager:

From extensive review of the adherence literature as well as from behavioral theory the principles and practice of the medication manager have been outlined.

Principles:

Work in partnership with the patient.
 Focus on individual strengths and achievements.
 Adherence behavior is driven by information and motivation.
 Honor skills, competencies, and talents.
 Exude a “can do” attitude.
 Foster self-efficacy and power.
 Recognize the contribution of the patient’s beliefs in the treatment and in their ability to adhere.
 Expect barriers.
 Monitor behaviors, not goals.
 Attribute positive behavior to the patient

Practices:

Identify:

The patient’s perceptions of illness, treatment, and barriers to adherence.
 Readiness for treatment and adherence
 Patient preferences
 Vulnerable times for non-adherent behavior.

Give information that is clear, written, and non-technical.
 Teach behavioral skills.

- Use return demonstration to evaluate adherence.
- Tailor the regimen to the patient, not the patient to the regimen.
- Have the patient develop their own goals and plan for achieving adherence.
- Have the patient practice organizing their medications and following a schedule in the home setting.
- Provide immediate feedback.
- Identify collaborators and a support network.
- Use visits to the patient's home for assessment, intervention, and identifying resources.
- Follow up with the patient at designated intervals.
- Use adherence tools-reminders, cues, and organizers.
- Contribute to patient satisfaction by acting as a liaison with the provider.

Each patient referred to the medication manager will be viewed as an individual with unique needs and circumstances. Therefore, the principles will remain consistent but the specifics of the practice will vary depending on the needs of the patient. Non-adherence in a patient who has a good support system but can not remember to take their medication will call for a different intervention than a patient who is homeless and non-adherent. The response to non-adherence also must vary depending on the patient's strengths, knowledge, and skills. The algorithm in Figure 3 serves as a guide for individualized medication management.

Figure 3: Medication Management for Non-Adherence

Motivational Barriers:

Beliefs → Assess, discuss, educate, liaison with provider.
 Locus of Control → Identify strengths, contract, set goals with patient.

Patient Satisfaction:

Identify clinic and provider barriers
 Liaison with provider

Regimen Barriers:

Access to Medication → Refer to case management/social service.
 Regimen Complexity → Teach organization, use organizer boxes, teach cues, use return demonstration.
 Side Effects → Liaison with provider.
 Interactions → Educate patient, tailor, establish schedule, liaison with provider.
 Regimen Intrusiveness → Review patients daily schedule, tailor.
 Lack of Knowledge → Provide information, clear, non-technical, written, use pictures.

Lack of Support:

Assess Potential Collaborators
 Identify Family/Friend Support
 Increase Supervision

Educate collaborators

Refer to AIDS s service organization, groups, buddies, case management

Readiness:

Assess Stage → See Table 11
 Liaison With Provider

Medication Manager Job Description:

1. Assess patient environmental, lifestyle, and functional barriers to adherence. Assess knowledge and motivation.
 - a. Home visits as necessary.
2. Develop an adherence support plan based on patient strengths
 - a. Reinforce patient understanding of disease process and the relationship of adherence to viral resistance.
 - b. Develop realistic medication schedule.
 - c. Work with patient to implement support system.
 - d. Teach patient adherence skills.
 - e. Assist patient to identify and manage impact of cultural beliefs on compliance
3. Monitor adherence and identify problems.
 - a. Document adherence and adherence problems (pill counts, patient reports, etc)
4. Serve as a liaison between patient and provider.
 - a. Notify provider of adherence problems and side effects.
 - b. Foster communication between the patient and the provider.
 - c. Accompany patient to medical visits as requested by patient.
5. Work collaboratively with other members of the health care team as needed.
6. Maintain database of additional available support services.
7. Document outcomes of services to patients
 - a. Develop database of patients served
 - b. Track and identify barriers to care. Other duties as necessary.

Anticipated Workload:

Follow 35-45 patients for up to 12 weeks with subsequent quarterly monitoring for up to 1 year. Minimum of one home visit per patient (when possible) to perform an initial assessment and develop an adherence plan. Minimum of weekly contact; more if necessary.

Qualifications:

Required: Excellent communication and interviewing skills. Creative problem solving skills. Flexibility. Non-judgmental attitude. Good people skills. Good judgement.

Desired:

Knowledgeable about HIV. Previous experience with HIV patients. Bi-lingual/bi-cultural. Experience working with addicts. Ability to assimilate rapidly changing medical information. Well organized. Own transportation. Health education or allied health background. Knowledge of basic medical terminology. College education or paraprofessional certificate.

A Case Study: Carmen and Albert

This thesis has illuminated the problems encountered in antiretroviral adherence

and has laid the foundation for the creation of a member of the health care team who can support adherence behaviors. As I wrote this paper I utilized the concepts, imagining myself as the medication manager, using newly gained knowledge to improve the adherence of the patients I follow in clinical trials. I would like to briefly share my experience with Carmen, one of the patients I follow. Carmen is a 26-year-old Latina woman from Bridgeport who was diagnosed earlier this year with HIV infection. She was asymptomatic and followed by a nurse practitioner in Bridgeport. Carmen came to Yale to be evaluated for participation in an antiretroviral clinical trial. She had a mid range viral load of 32,241 copies and a CD4 count of 375 and she had never been treated for HIV before. Her affect appeared giddy and flip, yet she had a serious concern about her health. In April we enrolled her in a study examining the safety and efficacy of a triple combination of nelfinavir/AZT/and 3TC. Carmen was on medication for 6 months when I inherited her as a study patient. In routine questioning about her adherence, she admitted that it had only been fair. This was supported by her fluctuating viral load and by the number of pills left in her medication bottles, which she dutifully brought to her study visits. In October, on her week 24 visit on study I decided to focus intensively on her medication adherence. I asked her to come in every four weeks so that we could work on her adherence, rather than every 8 weeks, according to protocol. I also asked her to bring her significant other to her next visit. When Carmen and her boyfriend, Albert, came for her visit, we spent several hours working on her adherence. We talked about how she felt about her medications. She told me how she hated the “nasty blue pills.” She never called them by name, always the “nasty blue pills.” I asked her to tell me what she does each minute of her day, beginning with her waking up. I wrote her schedule in

great detail, including her medication dosing times. I referred to her nelfinavir as the nasty blue pills, the 3TC as white diamonds, and the AZT as white circles, just as she does. I learned what was important to her during her day and I listened carefully to her responsibilities and became aware of her need for more control in her life. She told me that when all her responsibilities were done, she liked to go out at night. I asked her tell me which doses were hardest to take. It was of course the doses that fell during the time when she liked to go out. I involved her boyfriend Albert in the discussion and asked her and Albert to try and figure out how she could remember to take more of her pills. I witnessed them creating a plan and I supported their decision. They determined that the morning was a time that Carmen was faithful about taking her pills. They decided that when Carmen takes her morning pills she should also put the rest of the day's pills in a pouch, so that no matter where she was, she would have her pills with her. They also decided that she would fill an additional pouch with a one-day emergency supply of pills. They identified that no matter what Carmen is doing, she always carries her black knapsack. This was a safe place to keep the pills. I wrote down what Carmen and Albert had agreed to do to improve Carmen's adherence. I asked Carmen to sign the plan, indicating that she understood what she had agreed to do. I asked them to come back in four weeks for Carmen's regular study visit. They returned in four weeks and reported that things had gone much better. Carmen's viral load results arrived this week. Her viral load is below the limits of detection, for the standard assay, which measures down to 400 copies as well as by ultra sensitive assay, which measures down to less than 40 copies. I immediately called Carmen, to share the good news and to praise her for *her* hard work. This case represents a successful moment in a therapeutic relationship.

Again, we will not wait 8 weeks as required by the protocol. Carmen will return in 4 weeks to reinforce the process.

Key points about this intervention are supported by the literature. These include:

- More frequent visits
- Eliciting beliefs about her medicine.
- Identifying problem times.
- Involving a support person
- Showing respect.
- Having the solution come from the patient
- Having Carmen sign the plan, creating a behavioral contract.
- Immediate feedback upon receiving her viral load results. Behavioral “cheerleading”, an important concept in supporting adherence.
- Giving Carmen the credit for improving her adherence.

Improving Carmen’s adherence was easy due to the solid support of her boyfriend.

Most patients, however, do not have so easily identified a person who is as invested as Albert in their care. There isn’t anything that I did to help Carmen with her adherence that needed to be done by a nurse. On the other hand, there are few physicians who have the time to spend several hours with a patient. Under normal clinic conditions it would also have been impossible for a clinic nurse to have the time necessary to carefully evaluate and implement a plan to improve adherence.

Training the Medication Manager: A Curriculum

A curriculum has been designed based on review of the adherence literature and review of theoretical models of behavior. Relevant concepts from both have been translated into curriculum content. Training of the medication manager will emphasize respect of the client, and an understanding of the difficulties of organizing ones life around complex but life-saving medication regimens. Medication managers will be taught skills of assessment, problem solving, and client education methods. They will also be given sufficient

information on HIV infection and its treatment as well as the factors affecting adherence

Week I

General HIV Overview:

- Basics of the immune system (including T cells and their role, meaning of T cell counts)
- Pathogenesis (viral life cycle, concepts of replication, meaning of viral load)
- Natural History (Seroconversion and Primary Infection, Asymptomatic infection, Progression, and AIDS)
- Clinical Picture (Symptoms associated with HIV, what do T cell counts tell us about risk of infections, Major opportunistic infections)

Week II

HIV Treatment Strategies-Part I

- Basic concepts of HIV care
- Understanding HIV treatment approaches (including concepts of combination therapy, HAART)
- Classes of HIV Medications:
NRTIs, NNRTIs, Protease Inhibitors, Immune Based Therapies
- Treatment of Opportunistic Infections

Week III

HIV Treatment Strategies-Part II

- Specific medications
- Medication actions, medication side effects
- Medication interactions:
Drug:Drug interactions, Drug:Food Interactions
- Concepts of Resistance-simplified
- Mutations to Resistance 101

Week IV

Adherence

- Why is adherence important?
- Why is adherence difficult?
- Issues/Barriers in medication adherence (Patient, Provider, Environmental)
- Exploring cultural issues that relate to adherence
- Human Behavior 101

Week V

Integrating theoretical models into the practice of the medication manager

- Brief summary of behavioral models and what we have learned from them
- Health Belief/Decision Model
- Locus of Control Theory
- Strengths Model
- Transtheoretical Model of Change
- Information, Motivation, Belief

Week VI**Patient assessment**

- Beliefs and attitudes about HIV and treatment
- Identifying strengths
- Identifying weaknesses and vulnerable times
- Evaluating the environment, adherence potential, lifestyle, adherence support and functional barriers to adherence
- Tailoring, medication scheduling, and organization
- Developing an adherence support plan-who can help, how can they help, when can they help
- Evaluating needs for support (including how often to contact the patient)
- Strategies for improving medication adherence
- Monitoring adherence

Week VII**Patient education strategies-part I (What does the patient need to know)**

- General HIV information, side effects, drug interactions, food interactions
- Teaching patient adherence skills
- Supporting patient/provider communication

Week VIII**Patient education strategies-part II**

- How to involve your patient in the adherence process
- Role play
- Adherence problems (what are the signs and what to do when a problem is identified)
- Trouble shooting adherence problems (including when and how to call the provider)
- How to serve as a liaison between your patient and their provider
- Resources to assist medication managers

CONCLUSION

Non-adherence to antiretroviral therapy has been well-documented (Chesney, 1998; Gallant and Block, 1998; Johnston, 1998; Jiminez-Nacher, 1998). As HIV evolves into a chronic manageable disease the importance of medication adherence comes into light. While the study of adherence in HIV disease is in its infancy much has been learned about adherence from other chronic diseases, which can be applied to adhering to antiretroviral therapy. Medication adherence is known to be a factor of numerous variables including beliefs, preferences, readiness, social support, and relationship with provider. Information is necessary but not sufficient to assure adherence. Adherence also requires organizational and behavioral skills to be able to establish a medication taking routine.

Currently, adherence issues are generally addressed by the provider in the form of a question directed at a patient. There is conclusive evidence that the information gained by self-report is often inaccurate. This question may be followed-up by the adjustment of the medication schedule or perhaps a switch to a different regimen which seems to fit the patient's needs. This approach is unlikely resolve adherence issues given the limited question and answer approach that is feasible during a busy clinic session.

The literature has shown that single interventions to enhance adherence each have a small effect size and make little difference in overall adherence behavior. Adherence can be improved, however, with a combination approach utilizing educational, behavioral, and educational modalities. The existing HIV health care system is already stressed and can not provide patients with the added attention necessary to carry out a comprehensive plan to improve adherence. It is not only feasible but also important that

components of adherence enhancement become incorporated into the daily activities of providers. However, the magnitude and complexity of the adherence problem in the treatment of HIV disease is significant and warrants a comprehensive and organized approach.

This thesis proposes that the issues of adherence in individual patients can be managed best by the creation of an instrument that can enable us to apply the principles and practices identified to improve adherence. In this model a health care professional, called a medication manager, would become knowledgeable in evaluating factors which influence adherence and teaching behavioral skills necessary to take antiretroviral medications as prescribed. The medication manager would become the co-orchestrator of the adherence effort, acting in partnership with the patient and their physician. The medication manager would be trained to focus on influencing adherence behavior. This requires an ability to assess patient circumstances and attitudes, apply principles of behavior change and identify cues and supports to help patients adhere.

It is recognized that this model would require additional financial resources not currently available for the addition of a new health care position. It could be argued that we cannot justify the addition of a new health care professional in today's health care environment. There is also no data to support a cost:benefit argument in favor of a medication manager program. However, it is known that enormous resources have already been expended to develop medications to treat HIV infection. The failure of these medications and greatest waste of precious resources is largely related to patients not being able to take antiretroviral medications as prescribed. Before we judge our patient's value of medication adherence it may be important to begin by evaluating our

own value of adherence. It is our failure to adequately address issues of adherence that sends an important message to our patients and determines our commitment to the future of HIV care.

Appendix 1

Abstracts from the 12th AIDS Conference Geneva.

Type Legend: G=general; C/P=Characteristics of adherent/non-adherent and/or prevalence; I=intervention; F=Factors/barriers; A=adherence assessment; CQ=consequences of non-adherence; \$=Costs of non-adherence T=adherence theory

Author	Country	Type *	Study Focus	N	Findings
Chesney	USA	G	Overview		
Woodward	USA	C/P	Demographic		
Workman	Australia	G	Overview		
Bangsberg	USA	C/P	Homeless	154	VL ↓ in adherent only, drug levels consistent with reported adherence
Nakashima	USA	C/P	Frequency of adherence	1,274	2/3 reported always, less in IDUs, adherence decreased over time
Turner	USA	C/P	prevalence in IDUs	727	no difference between active and non active IDUs
Ferrer	Spain	C/P	discontinuation rate of PIs	230	High proportion dc in first 6 months, counseling needed
Walsh	UK	C/P F	Prevalence, lifestyle, health beliefs	114	Assessment by pt., MD, pharmacy records, interviewer. Full adherence in 41%. 25% were < 80% adherent.
Hogg	Canada	C/P	Virologic response in IDUs vs non IDUs	806	IDUs 43% less likely to have pVL <500(or=0.57,95% CI, 0.35-0.93); less likely to be adherent (p < 0.001)
Johnston	USA	C/P F	Interview of inner city pts.	198	56% took meds irregularly or not at all. Reasons: 69% side effects, 43% felt meds would do harm, 26% regimen too much trouble, 21% felt meds would not work.

Author	Country	Type*	Study Focus	N	Findings
Turner	USA	C/P	HIV + women post delivery.	696	ART use increased between 1994 and 1995 in inner city women. Full adherence varied by race, delivery site, prenatal care.
Jhingran	USA	C/P F	Adherence to abacavir/combivir/amprenavir	24	Missed RTI as often as PI. Barriers: hard to swallow
Gifford	USA	C/P F	Adherence in pts enrolled in HIV education program	57	52% adherent. Adherent pts had lower CD4s, were less likely to contact their MD. Beliefs for adherent: meds fit into my daily routine, my HIV is responding to meds, I will be able to take meds as instructed.
Hedge	UK	C/P F	Knowledge compared to behavior		Good knowledge >85%, adherence to meds with diet restrictions 50%, adherence to meds with no diet restrictions 95%. Barriers: work schedules, lunchtime doses, food requirements.
Carrieri	France	C/P F	Comparison of adherence in IDUs who are taking ART therapy with and without PIs	66	Full compliance was found in 72% and not associated with PI or non PI use. Pts hospitalized within the past 6 months more compliant ($p=0.003$). 56% compliance in women, 75% in men. Factors: too busy, asleep, forgot. Suggest more frequent contact with staff.
Brigido	Brazil	C/P F	Retrospective, uncontrolled chart review from HIV clinic	82	Less than 50% fully compliant. 20% forgot, 15% disbelief in the meds, 12% stopped for weekend drinking. <20% cited side effects as reason for non-adherence.

Author	Country	Type*	Study Focus	N	Findings
Ohmit	USA	C/P F	Women at the HERS & WHHS sites	196	50 % fully compliant, 25% took >75%, 10% took 50-75%, 10% took 25-50%. Factors: forgot (57%), side effects (39%), dis belief in the meds (20%). Black race (p 0.018), recent IDU (p 0.07) associated with poorer adherence,
Nieuwkerk	Netherlands	I	Questionnaire administered at 4 time-points in 48 weeks to compare adherence in a 2 drug vs a 3 drug BID regimen.	126	# of days skipped # of days off by > 2hours # of days fasting not followed
Williams	USA	C/P F	Interview survey of women in on-going clinical trial.	89	Range of adherence 0-100%. 54% took 97% of meds. + Predictors: no current drug use (p=0.02), no side effects (p= 0.03), stable living (p=0.008), feeling MD spent time during visit (p=0.03), understanding of the purpose of ART
Ostrop	Canada	F	Prescription fill data & 2 questionnaires to measure compliance and change in compliance over time	100	# of meds-no significant impact. Factors: compliance tools, side effects, regimen design, pts attitude about treatment
Heinasmaki	USA	C/P F	Adherence & adherence indicators compared in clinic v. clinical trials pts	84	Self-report: clinic 80% v. trials pts 89% adherence. Pill count: 73% clinic v. 95% clinical trials. ↓ VL and ↑ CD4 not significant
Bachiller	Spain	C/P F	Pharmacist based questionnaire, review of refills	567	85% compliance with regimens. Factors: psychiatric problems, poor understanding of the regimens, side effects, and regimen complexity

Author	Country	Type*	Study Focus	N	Findings
Burgos	Argentina	C/P F	Survey	179	43% full compliance, 30% interrupted regimen for at least one day. Factors: 24% problems getting meds renewed, 20% avoiding side effects in key situations; 17% work place med taking or storage problems, 9% learning of others med failures, or others worsening illness or death
Kreitchman	Brazil	C/P F	Adherence questionnaire concerning ART prophylaxis for vertical transmission	64	Non adherence strongly related to having prior infected children or an infected partner (OR 2.0). Adherence better with the use of drugs other than AZT (OR 4.67)
Ford	Canada	C/P	Degree of adherence for pts adding Saquinavir to two ARTs.	44	9% regularly missed 1-5 doses/week, 16% missed regularly missed more than 5 doses/week, 62% did not miss any consecutive doses, 20% had stopped for >2days on at least 1 occasion.
Gir	USA	C/P	Four country questionnaire. Factors associated with adherence in different cultures.	235	46% of pts surveyed forgot to take meds on occasion. No difference among the four centers.
Martinez	PR USA	C/P	Comparison of double vs triple therapy	NG	Significant difference seen in adherence between double and triple therapy regimens
Bergeron, Gormley, Sousa	USA	C/P	Viral load used as a measure of adherence to compare clinical trials pts to clinic pts	87	84% of clinical trials pts had pVL < 400 compared to 59% of pts receiving meds by prescription (60% when only looking at naive pts)
Ross	USA	C/P F \$	Inpatient interview of pts admitted within past 33 days & outpt chart review	23	Adherence was poor in 14/23, fair in 4/23, good in 5/23 based on compliance score system. Pill burden ranged from 7-108 pills per week

Author	Country	Type*	Study Focus	N	Findings
Workman	Australia	C/P I	Anonymous questionnaire after adherence interventions implemented	77	73% reported 100% adherence, 26% reported 80-100% adherence, 1% reported 60-80%. Adherence not related to number of meds in regimen or dosing schedule Interventions: Extended consultation, tailoring regimen to lifestyle, frequent follow-up, reminder calls, alarms, and rapid viral load feedback
Ladd	Canada	T	Description of a new framework to improve the study of adherence		A tripartite model involving the task to be performed, the person performing it, and the setting or context in which it is performed. By controlling the influence of any 2 components in this model the 3rd can be studied.
Schilder	Canada	T	Focus groups and interviews	47	Results: pts overwhelmed by new info, requesting plainer, less technical language. Scheduling, dosing, and side effects primary interest.
Harley	USA	T	Review of written materials to analyze the focus of responsibility in relation to adherence		Need for a more balanced discussion of meds that includes the limitations of current regimens so that less blame is placed on the pt if treatment fails
Frank	USA	I	Development of a comprehensive training program to assure that prison staff emphasize the importance of adherence to HIV infected prisoners		Provider education on new treatments and adherence principles, peer based inmate education, and early identification of infected inmates can enhance inmate care and improve adherence

Author	Country	Type*	Study Focus	N	Findings
Vallier	USA	I	A collaborative statewide effort to address adherence issues by convening a working group of MDs, nurses, social workers, pharmaceutical representatives, and state and local govt.		The development of adherence tools, access to help in scheduling, provide standardized training to Hotline volunteers, case managers, and other state personnel. Adherence video, fact sheet, and training developed.
Tuldra	Spain	I	Controlled randomized study. Two groups: intervention vs no intervention followed by interview	53	InterventionGroup: counseled on how to take meds and tested on the regimen vs just tested on the regimen. No difference between study groups ($p=0.26$) but higher compliance in study groups (95%) than in those not in either study group.
Ebere	USA	I	Impact of Tools for Health & Empowerment course on med adherence. Eleven module education program	32	Pre and post intervention data on 4 variables: frequency of missing 1 PI dose, missing all PI doses, physical effects, total score s.s. improvement after intervention ($p<0.05$)
Scott-Lennox	USA	I	Focus groups and interviews conducted to development of a brief self report to evaluate care.	31	#1 priority MD competence, #2 pt provider relationship. Participants related satisfaction with care to adherence. Adherence may be improved by providers recognizing the connection with satisfaction with care
Arima	Japan	I	Prospective nurse administered questionnaire and interview concerning knowledge, beliefs, compliance, and barriers.	60	Early on in treatment adherence associated with side effects, in the second period pts who understood the regimen and the difficulties in continuing meds adhered, over time pts in touch with their own difficulty with the meds adhered

Author	Country	Type*	Study Focus	N	Findings
Cruz	Brazil	I	Small anecdotal experience using home care staff to evaluate threats to adherence		Positive results, no data
Corpron	USA	I	Nurses met with pts to assess barriers to adherence and provide resources.		Verbal reinforcement (100%), printed med info (84%), viral load/CD4 info (63%), pillboxes/med schedules (28%).
Wood	USA	I	Social work assessment to include adherence needs and deficits. Discussed in multidisciplinary rounds. Link with the community based on needs.		Pts became more involved in their care through collaborative problem solving interventions.
Le Coz	France	I	Telephone survey conducted to assess adherence	20	ver missed a dose. These responders had high info and were very involved in the HIV nity. Reasons for missing doses: #1 simply #2 fatigue or changes in daily routines like way from home. #3=side effects. #1 dose 1st afternoon dose, #2=late evening dose. unsealing protocols developed.
Haberl	Germany	I	Once daily dosing with nevirapine/ddI/3TC in IDUs	70	An increase in methadone was required in 13 pts. Six pts dropped without explanation. At week 24 > 90% of pts had undetectable VL.

Author	Country	Type*	Study Focus	N	Findings
Broadhead	USA	I	Peer driven intervention for IDUs. Health advocates assigned to peers. Meetings once/week to assess adherence using questionnaire. Rewards earned by advocates for positive peer behavior.	14	Peers kept 95% of appointments with clinicians and advocates. Adherence scores for previous week measured 80% or better. No drop outs. Positive results with an alternative support structure.
Graham	USA	I	Pts with a history of non-compliance or at risk for non-compliance referred to a pharmacist for adherence counseling at the start of meds.	122	Mean 1.6 visits/pt. Interventions included side effect management (21%), change interval/schedule (17%) dosage adjustments (12%), schedule with/without food (7%), less pills taken than prescribed (6..5%), drug interaction (5%), illiterate/language barrier (5%). Before vs after pVL <400 Naïve:0%vs 52%, Nucleoside experienced 0 vs 48%, PI experienced 13% vs 45%.
Knobel	Spain	I	Pharmacy intervention	186	Conventional dispensing of meds: 52% adherence, pharmacy intervention: 77 % adherence (p.0005). Undetectable pVL Conventional: 56%, pharmacy intervention: 63% (p.1)
Rohr	Switzerland	I	Free newsletter published by community agency to bridge the gap between providers and community and to bring info to pts.		Newsletter well received. No data provided.

Author	Country	Type*	Study Focus	N	Findings
Kunches	USA	I	Focus groups to assess adherence, treatment awareness and needs	50	50% took 90% or more of meds correctly in previous month. Intense pressure from friends, family, providers resulted in fear of failure. Fear of asking “dumb” questions drove decisions to postpone seeking help. Good social support and high levels of personal motivation cited as important in adherence. Programs should address: knowledge (dosing times, storage, and interactions) and skills (organizing schedules, managing side effects). Clinics should have independent support for adherence.
Woodward	USA	I	Descriptive study of pt choice of HAART	141	Pt choice of HAART: RTV 73%, over IDV 22 % . Pts changing meds: 57% on RTV vs 43% on IDV Pts chose BID (66%) over TID (33%),
Esch	USA	I	Genotypic and Chart review of HAART non-responders to determine the effect of med adherence enhancement	64	Despite pt self report of adherence, viral genotyping suggest non-adherence in 45% . Thirty six %
Nemecheck	USA	I	Survey to evaluate pharmacy related resources and their impact on adherence	45	98% surveyed on a med regimen. Adherence seen as important in 88%. Barriers: meds not covered under their insurance (35%), must travel >21 miles for medical treatment (40%), must travel > 21 miles to pharmacy (15%), funding issues (17%). Case management services important to resolve issues that impact adherence.

Author	Country	Type*	Study Focus	N	Findings
Farnsworth	USA	I	A program was developed to increase adherence in pts on BID vs TID regimen. Intervention= medication management (pill box, instruction card) & pt. support (pt planner, newsletter, graphs of VL & CD4).	27	Pts on a nelfinavir/saquinavir/d4T/3TC regimen BID vs TID responded well to interventions. The median daily dose for the BID group was 2430(full dose= 2500 mg/day). The median daily dose for the TID group was 2100 mg/day (full dose= 2250).
Therrien	Canada	I	HIV Medication Guide developed to enable providers and pts to develop a medication administration schedule that fits into an individuals routine		The Guide designs individualized , optimal drug administrations schedules, detects drug interactions and offers appropriate nutritional and pharmaceutical tips on how to alleviate some side effects and improve compliance.
Manheimer	USA	I	Prospective intervention to assess the impact of the ALR (a little reminder alarm).	49	Frequency of 100% pill, time, & diet adherence- (p<.001) Baseline: 25% ; 1 month: 67% ; 3 months: 89% Frequency of 80% time adherence (p<.001)- Baseline: 35%; 1 month: 92%; 3 months: 94% In this study high school education correlated with adherence (p<.05) & former IDU (p<.05), current IDU(p<.005) correlated with non=adherence
Ward	UK	I	Two mass media campaigns launched and compared to establish recognition, understanding, and the impact on personal decision making		Semi structured interviews conducted first campaign achieved 100% recognition, both had 50% recall by participants, and 100% understanding on reminder. No data for impact on adherence.

Author	Country	Type*	Study Focus	N	Findings
Schilder	Canada	I	Data collection through 2 peer facilitated focus groups to identify barriers to health care acceptance and adherence in transgendered addicts	10	Barriers to health care identified: abuse by providers, pts avoided care until hospitalization required. Failure in professional skill, practice, lack of cultural competence. Poor relationships with providers. Care failed to nurture their self concept as women. Adherence is improved when gender care is coordinated with addiction care. The need for hormone therapy is an important point of entry into health care.
Byrd	USA	I	Six month observational study to determine effectiveness with automation technology, counselor calls.	80	Improvement in adherence achieved. Data pending.
Hernandez	USA	I	Prospective cohort study to evaluate impact of adherence counseling by nurse educator, pharmacist, and an ID physician.	87	
Nissan	USA	I	Pts provided with a monthly compliance checklist. Adherence data received via phone if pts don't return results. Results divided by 3 levels of adherence each associated with specific intervention. Counseling, social services, and MD consult available.		No data. Systematic process of assessment, identification of factors contributing to non adherence, and tailored interventions developed.

Author	Country	Type*	Study Focus	N	Findings
Pratt	UK	A, F	Associations between adherence and personal and clinical variables, engagement with providers	270	Two different adherence measures significantly correlated with each other (Reported Adherence to Medication Scale, RAM, and Morisky Medication Adherence Scale, MMAS)($p<0.0001$). Perception of meds decreasing VL (MMAS $p0.008$). Adherence poorer in those living alone($p=0.05$)
Pernerstorfer-Schoen	Austria	I	Once daily dosing of nevirapine/ddI/3TC given to antiretroviral naïve pts unwilling or unable to take BID or TID regimens	18	Baseline RNA 3.23 to $>5.8 \log_{10}$ copies/ml. At week 6, 55% were below limit detection (<200), and a subset of 6 pts had VL < 50 . 5/18 discontinued meds due to rashes and liver enzyme elevations. This regimen may be an option for pts with limited adherence
Shaffer	Thailand	I	Randomized double blind placebo trial using a higher dose of AZT BID starting at 36wks gestation to improve adherence to vertical transmission prophylaxis	397	This regimen is safe and well tolerated. Data on efficacy is pending. Study drug adherence and follow-up were extremely high.
Griffaz-Mauris	France	I	Info given about meds, virus, side effects, nutrition. Nurse educational follow-up, access to psychologist/psychiatrist, pill box and pill diary given. Pts connected with a network to meet others on treatment. Side effects treated quickly, access to staff for questions.	173	Reported benefit from increased communication and mutual understanding. No data.

Author	Country	Type*	Study Focus	N	Findings
Powell-Cope	USA	F	Survey to assess relationship to professional support to adherence. Engagement with Health Care Provider, Caring, and Satisfaction with Care scales used.	727	Perceived professional support explained 19% of the variance in follows advice in instructions (caring explained 15.7%; engagement 2.6%, satisfaction .6%). Perceived caring was significantly related to med adherence explaining 3% of the variance.
Lubin	USA	I	National adherence initiative to attain consensus on education, training, medical, behavioral, social, and family support needs		Priorities identified: pt education materials, clinician training and assessment tools, adherence curricula, acquisition of adherence knowledge from other diseases and strategies to address adherence training for policy makers, legislators, and payers.
Waters	USA	I	Support of a demonstration project of 3-6 innovative models to improve adherence in special populations. Programs required to integrate medical and non-medical service providers to		No data.
Quirk	UK	F	Structured interviews to determine barriers to adherence.	70	Not enough info given at start of meds, regimens disruptive to life. Specialist support for adherence seen as important. Early intervention for side effects may avert therapy stop. Timely feedback between pt and provider may enhance adherence.

Author	Country	Type*	Study Focus	N	Findings
Hedge	UK	I	Single session informational and problem solving groups offered to improve adherence with meds and decrease use of recreational substances, which could interact with HIV meds.		Pts encouraged to take a problem solving approach to drug related and lifestyle. Groups judged useful by 75% of participants with requests for further groups issues. No data.
Brown	USA	F	Descriptive survey to determine relationship of social support to adherence. Four measures of social support used and 3 measures of adherence.	727	5.6% of the variance in med adherence was explained by social functioning (4.6%) and perceived social support (1%). 10% of the variance in following advice and instruction was explained by social functioning (8.7%) and perceived social support (1.4%). A significant but modest relationship between the
Fegueux	France	I	Information disseminated to general practitioners and pharmacists sponsored by the government. Training provided to pharmacists on treatment, adherence, good practices, and confidentiality. Three year research initiative on adherence.		The French government has made access to treatment and adherence a public health priority. Highlights the importance of a multidisciplinary approach.

Author	Country	Type*	Study Focus	N	Findings
Lamp	European collaborative	I	Video produced by people with HIV and the European Collaborative to educate people with HIV about viral mechanisms and adherence. Disease stigma, scheduling, interactions, and side effects included. Pts interviewed to share suggestions for coping.		Demonstrates the importance of a collaborative effort in producing educational materials. Viewer survey pending.
Grahame-Smith	UK	I	HIV positive volunteers trained on HIV and group skills. Workshops include basic science, immune system, disease progression, treatment, side effects, resistance, and adherence.	354	Thirty two workshops run: 100% of participants would recommend the course, 67% felt topics covered well, 49% said basic science was their favorite section. Highlights the value of using non-medical people in trainings.
Vilas	Brazil	F	Twenty four-month patient follow-up study to identify professional practices which contribute to non-adherence in med taking. Pt interviews, counseling sessions, interviews with providers.	34	Barriers identified: 1-incomplete information taken by providers on pts. work, family, and social structure, 2-lack of acknowledgement of provider prejudice, 3-insufficient appointment time, 4-no services available for dealing with pt doubts about treatment, 5-no cross disciplinary communication. Recognition of these issues improved #1,2, 5. 47% increase in adherence.

Author	Country	Type*	Study Focus	N	Findings
Hannan	Australia	I	Training program developed to educate Health and Support Workers on treatment issues using a psychosocial spin. Included skills in client enablement and set in the context of pts lives.		Participation of HIV positive people and structuring treatment information around psychosocial context essential to the success of this program.
Esch	USA	I	Development of a pharmaceutical care specialist program to educate, coach, & problem solve. Pt referrals for drug interactions, increasing VL, new regimen, poor adherence, adverse drug reactions, interpretation of genotype results.	89	Many referrals, data pending.
Alcorn	UK	I	Community based HIV & AIDS Treatment Directory and monthly factsheets published. Training program, monthly forums, and self help groups held.		Community based but supported by the medical community highlighting the importance of this partnership.
Whittaker	Australia	I	Collaborative effort by activists, providers, and researchers to produce a booklet to improve adherence. Covers: diet, dosage times, and scheduling meds into lifestyles, and commonly asked questions.		Produced with limited funds and resources. Self testing quiz included to help patients identify the drug combination which suits their needs. Distributed to places of care and community based organizations. Well received adherence resource.

Author	Country	Type*	Study Focus	N	Findings
Colon	USA	I	A one day conference on adherence for non-medical service providers (case managers, health educators, peer educators, and treatment advocates).	40	Issues presented and work groups established to identify barriers and strategies. Well received by participants. Highlights the importance of a collaborative approach.
Foisy	Canada	I	Development of an HIV therapy scheduler for providers. Goals: develop customized regimens, screen for potential drug interactions, and store pt med histories		Database containing 2165 active drugs with 2799 possible drug/drug reactions, 70 drug monographs, medication dosing guidelines, and rapid access drug info tool. No data
Salicru	France	I	Fifty questions survey to compare provider vs pts assessment of adherence of pts in "social difficulties" vs those in "good social situations".	193	Providers assessment: 88% of pts in good social situations adhere vs 35% of those with difficulties Pts assessment: 77% of pts in good social situations vs 21% with difficulties. Barriers to adherence: to disclaim disease (16%), despair (16%), and due to weekend or holiday travel (33%).
Marston	USA	I	Statewide effort to develop innovative programs to improve adherence. Will include a standardized adherence survey to be used at each of the 15 sites.		Data pending.

Author	Country	Type*	Study Focus	N	Findings
Shelton	USA	I	Computerization of ART use, adherence, and tolerance. Pt asked about adherence on clinic visit.		All meds and med changes, adherence, and surrogate marker data input weekly. Surrogate marker data interpreted by a pharmacy specialist using the database. Doses missed in the past 48 hours recorded. Results of quarterly review of missed doses (in 753 clinic visits): no missed doses (44%), a single missed dose (43%), more than a single missed dose (13%). VL and CD4 data. Data base reduces time needed to evaluate viral load response.
Jones	USA	I	Directly observed ART therapy given to co-infected TB pts. One dose each day is administered by DOT and other doses for the day are organized by the community worker.	6	DOT has been successful in the treatment of TB and represents an option of improving adherence to antiretroviral therapy.
Leake	UK	I	Pharmacy led therapy clinic	79	Following consultation 2 yr data available: 54% remain on same regimen, 17% changed due to intolerance/toxicity, 18% switched due to virologic failure, and 6% stopped therapy.

Author	Country	Type*	Study Focus	N	Findings
Gonzalez-Lakoz	Spain	I	Safety and efficacy of ddI /3TC (both once daily) and /indinavir (twice daily) evaluated	32	Mean baseline viral load 70,080. After 3 months only 3 pts had detectable viral load (91% undetectable). Only one pt had to be withdrawn due to side effects. Pts chose schedules of their convenience avoiding mixing ddI and indinavir together.
Hupkens	Holland	I	National meeting was organized to initiate a collaborative effort to address adherence issues.		Strategic planning in progress.
Igboko	USA	I	T.H.E. (tools for health empowerment) course designed to improve adherence and quality of life. Includes knowledge, skills, attitudes. Collaborative effort.	190	Completion rate at 4 sites 80% after 11 weeks. Reported significant improvement in adherence post intervention.
Goetz	USA	F/T	Prospective controlled knowledge, attitude, and adherence behavior study based on the health belief model in diverse population	70	African Americans perceived greater barriers to care (p .0049), had lower clinic attendance (p 0.0084) and had higher baseline VL (p 0.019). Perceptions of susceptibility to progression correlated with belief in therapy (p <0.001) and concerns of disease severity (p<0.0001). Ethnicity, IDU, or psych history did not correlate with response to therapy after 6 months on therapy.

Author	Country	Type*	Study Focus	N	Findings
Agnoletto	Italy	F	Observational cohort study to evaluate level of adherence and correlation to the treatment, provider, and personal characteristics.	350	Baseline and 3 follow-up visits conducted. Study ongoing, results pending.
Paiva	Brazil/ USA	C/P	Questionnaire on adherence	100	Adherence rate: 41% for AZT, 45% for ddI, 21% for ddC, 52% for d4T, 56% for 3TC, 54% for Saquinavir, 31% for indinavir, and 44% for ritonavir. Reasons for non-adherence #1 forgot (35%), #2 situational obstacles (15%), #3 side effects (9%)
Arabe	Brazil	C/P	Retrospective study of patients receiving care at the free Ministry of Health Clinic	47	Total adherence in 53%, partial adherence (<1 week) in 21%, and interruption (> 1 week) of dosing in 26%. Reasons for non-adherence forgot (17%), delay in receiving drugs (9.4%), and intolerance (9.4%). Adherence in men 68%, women 30% (p=0.005). No difference among races.
Lorenzen	Germany	P/F	Prospective study, anonymous questionnaire to analyze adherence. Median duration on meds 23 months	214	56% deviated from regimen at least 1 day in the last week. No differences accounted for in # of pills, # doses, duration of meds, CD4 or VL. Reasons for non-adherence – forgot (59%), 33% sick, 19% side effects or not enough info re side effects

Author	Country	Type*	Study Focus	N	Findings
Jones	Ireland	F	Qualitative, semi-structured questionnaire to identify social, personal clinical factors of adherence in IDUs	23	Factors affecting starting meds- attitude toward HIV, support from family/partner, state of health, positive info about ART, conversations with providers. Factors affecting staying on meds- attitude toward future, good relationship with med team, belief that meds improve survival, belief that meds help drug abstinence, being in prison
Youle	UK	P/F	Retrospective study to determine reasons for med d/c in patients on triple therapy	505	35% stopped meds after a mean of 4 months. Reasons: Failure of indinavir (26%), nausea on ritonavir (32%), and failure of saquinavir. The likelihood of d/c decreased after 6 months on meds
Corless	USA	F	Descriptive survey to determine the relationship of cognition to adherence. Perceptions of cognition measured by standardized questionnaire, Morisky adherence scale used. Mean CD4 323, mean age 39.	727	Difficulty concentrating explained 4.9% of the variance in adherence, confusion explained 3.2% of the variance. Confusion explained 3.2% of the variance in missed appointments. Forgetfulness and difficulty concentrating explained 6.6% of the variance in following advice and instruction. Conclusions-self perceived problems with cognition impact on ability to adhere to meds
Klosinski	USA	F	Cross-sectional, mail administered survey on adherence. Non-adherence = not taking meds exactly as prescribed in past 7 days	1,322	Predictors of non-adherence: younger age, govt. subsidized insurance, extreme anxiety, extreme pain, and no change in health status. Level of education and income not predictive

Author	Country	Type*	Study Focus	N	Findings
Belzer	USA	P/F	Questionnaire in youth on HIV meds > 3 months enrolled. Demographic info collected	31	61% took meds at least 90% of time, 87% at least 75%. VL decreased to undetectable in 39%, another 26 % had at least 1 log drop. Homelessness, current living situation, education, depression, IDU, did not predict adherence. Pts closely supervised, well supported.
Bennett	USA	F	Seven focus group conducted to identify barriers to adherence. Qualitative and quantitative methods and self-report questionnaire	44	Logistical issues not paramount. Ecological perspective on adherence taken. Individuals highly stigmatized, marginalized, and lack access to care. Attention to logistical problems alone will not improve adherence. Must fit treatment between the person and their environment.
Weidle	USA	P/F	Cross-sectional analysis via anonymous questionnaire	72	28% reported non-adherence on the preceding day, 37% in the past month. Those reporting non-adherence on the preceding day were 9.9 times more likely to report non-adherence in past month. 29 persons gave 50 reasons for non-adherence. #1-toxicity (28% of reasons), lack of meds (26%) forgetfulness (24%). Drugs and etoh not associated with non-adherence.
Holzemer	USA	F	Descriptive survey to determine affect of psychological well being on adherence. Morisky Adherence Scale, follows health care advice, and missed appts scales used.	727	Psychological support (by 3 measures: cherishing the environment (CTE), fear zone, and role/emotional) explained 9.6% of the variance in adherence. CTE scale includes feeling comfortable and well cared for and having a meaningful life. CTE consistent across all outcomes.

Author	Country	Type*	Study Focus	N	Findings
Edlin	USA	F	Qualitative interviews every 6 months from 10/97-3/98 of street recruited IDUs.	64	Of 64 positive, 40% had ever received protease inhibitors. Barriers to adherence: homelessness, side effects, guilt, fears. Positive correlates with adherence: clear info about meds, accessible clinic, housing, pocket-sized pill dispensers, cash incentives and good relationship with provider.
Figueiredo	Brazil	F	Interview and survey on adherence.	61	Barriers to adherence: side effects (48%) # of meds (26%), combinations of drugs (26%) and fasting requirements (21%). Instructions not understood by 26% of pts. Drugs which generate most errors: ddI (20%) and indinavir (20%). Correlates include: amount of education and number of meds
Arboleda	USA	I	Workshops on choosing therapies and tools of adherence given to inmates.		Inmates adherence improve after having a better understanding of HIV treatment.
Halkitis	USA	F	Quantitative survey use of meds, adherence, and variables	184	Those taking alternative regimens, HIV symptoms, and perception of difficulty taking meds had higher rates of non-adherence, Adherence not correlated with sociodemographic, sexual activity, alcohol and drug use, psychological variables.
Schilder	Canada	F	Focus groups and interviews of gay youth	5	Barriers to adherence were conflicts in dosing and dietary schedules impeded participation in community life, which undermined identity.

Author	Country	Type*	Study Focus	N	Findings
Brieger	Germany	F	Small pilot study using interviews to identify pt views on self-disclosure and trust in physician		
Goldenberg	Brazil	F	Twelve open structured interviews to identify factors including socio-economical, emotional, cultural		"Adherence depends on determined life conditions". No data.
Kosko	USA	F	Descriptive, phenomenological design with interviews of HIV + women and 10 nurses to explore perceptions	20	Barriers to adherence: HIV + women cited child care and confidentiality. Transportation and family support enhanced adherence. Nurses identified IDU and chaotic lifestyles as barriers and IDU treatment and primary care as interventions
Nemechek	USA	F	Focus group with patients HIV+ > 5 years to determine issues of adherence	30	Primary source of knowledge from provider, none used pharmacist. Most difficult adherence times-weekends and mid-day dose. Complex dosing schedules and # of
Hirschhorn	USA	F	Retrospective chart review of use of HAART in community center to	72	58% did not achieve durable response. Barriers to durable response include advanced disease, more likely to have side effects (62% vs 30%, $p=.008$), and poor
Weiss	USA/ Netherlands	F	Adherence coded on a 6 point scale based on the results of 15 theoretical	40	Poor adherence related to more skeptical attitude towards HAART ($p=.003$), younger age $p=.048$), longer time on HAART ($p=.081$)
Stone	USA	C/F	Structured interviews and medical record reviews of diverse urban patients.	248	93% aware of importance of adherence. 50% of patients missed < 1/wk. Reasons for non-adherence- forgot(36%) felling sick (13%), too busy (7%). 66%

Author	Country	Type*	Study Focus	N	Findings
Nokes	USA	C/P F	Descriptive survey on adherence at 7 sites in USA. Adherence measured with	727	No gender differences found. Non-adherence in 58%. Reason- forgot. Women had decreased VL and higher CD4.
Pratt	UK	F	Interviewer administered instruments used to evaluate self-reports of adherence. Pilot study examining barriers to adherence in women. cognitive	120	RAM and MMAS correlated with each other ($p<0.001$). Pts perception of successful treatment ($p<0.008$), improved sexual drive ($p<0.02$), and Reasons for non-adherence-#1 demands of home or work (being busy) (50%), fatigue and falling asleep(38%), wanting to avoid side effects (22%), illness
Stone	USA	F	Multi-center study at 5 urban sites. Structured interviews and chart	248	41% d/c at least one P.I., 45% got 2nd PI and 50% d/c that. Reasons: Most due to GI and systemic side effects and treatment failure. Interventions should
Campbell	UK	F	Physician rated measurement of adherence developed for adherence	31	Relationships, domestic arrangements, social support, alcohol and drug use, knowledge about, satisfaction with, and attitudes toward meds.
Hales	Australia	A/F	Pts randomized to the addition of 1 pill twice a day (A) versus 1 pill 3 times a day (B). Questionnaire and pill counts administered.		Pts reported missing 5% of pills but had not taken 16% by pill count for A and reported 5% and missed 17% by pill count for B. Patients overestimate. Reasons for non-adherence: #1 forgot, # 2 did not have pills at necessary time, #3 not in their normal routine.
Hewitt	USA	A	Retrospective chart review of genotype results and whether med change was initiated based on genotype and if virologic response followed	64	68 genotype results were reviewed. 11 samples could not be amplified. Of 57 remaining, 37 regimens were changed after receiving genotype. 9 pts had no VL post change. Of the pts with follow-up 42% responded within 4 wks.

Author	Country	Type*	Study Focus	N	Findings
Ines	Brazil	A	Multi-center study of a multi faceted quantitative and qualitative method of evaluating adherence to identify factors and pts vulnerable to non-adherence		No data
Haubrich	USA	I/A	Randomized trial of intense VL measurement ($>6x/yr$) versus mostly CD4 monitored + VL 2x/yr.. Self-questionnaire at 0,2, and 6 months. Use of drugs and alcohol also evaluated.		Neither frequent viral loads, CD4 measurement, nor satisfaction with provider influenced adherence ($p>.05$) at 6 months . Use of drugs or alcohol reduced adherence (47% vs 84%, $p .0006$) at 6 months. Pts with consistent adherence had sustained VL suppression.
Gordillo	Spain/ Columbia	A	Descriptive, longitudinal study. Indirect methods: questionnaire about health	500	Significant differences were found between indirect and direct measures. More than 75% of patients had discrepancies in these 2 methods of assessment.
Hugen	Netherlands	A	Indinavir levels measured in saliva and plasma every hour from 0-8 hours by	14	126 paired samples analyzed. Either plasma or saliva levels could not be measured in 22 samples because levels were too low (esp 7-8hrs after dose. For 103
Tuldra	Spain	A/F	Longitudinal controlled study to assess use of perceived adjustment scale	81	Pts on ritonavir have more difficulty than those on saquinavir or indinavir. Most common reasons for difficulty:side effects and regimen complexity.
Woodward	USA	A/ CQ	Prescription refill and VL data reviewed	73	Worsening adherence significantly associated with decrease in VL ($p<.001$). Prescription refill data useful in assessing adherence.

Author	Country	Type*	Study Focus	N	Findings
Richter	USA	CQ	A Monte Carlo simulation was performed for each pt to predict VL, CD4, AIDS Progression, survival, and drug ,medical care and testing costs.	5,000	Under simulated conditions predictions were made for pts who adhered 0%, 20%,40% and 60% of the time for slow, fast, or average disease progressors. Results similar to quality of adjusted life years with sizable differences in life expectancy for adherent and non-adherent.
Marshall	USA	CQ	Observational study from a clinical practice database to assess impact of adherence at baseline on outcomes.	1090	Compared measures of survival, progression to AIDS, clinical events,change in surrogate markers, hospital days, and total costs of care and found no difference in adherent and non-adherent patients. No information on adherence available.
Tebas	USA	A	Retrospective study of evaluation of early adherence parameters to	66	Pills counts (p0.009), random AZT levels and viral load log decay (p0.008) at 4 weeks were useful predictors of HAART success at 6 months
Jiminez-Nacher	Spain	CQ/P	Pill counts done by pharmacist	135	An average of 78% of pts were adherent. 80% adherence was only seen in 56% of pts. Worse adherence was not seen with greater # of pills
Tamalet	France	A	Open label study of HIV pts to assess degree of adherence and resistance mutations prior to start of therapy.	30	Maximum CD4 response seen at month 9 in adherent pts. Undetectable VL at month 6 in 79% of adherent pts. Mutations prior to treatment did not prevent VL from decreasing. Non further mutations emerged in adherent pts.

References

- Abernathy JD. The problem of non-compliance in long-term anti-hypertensive therapy. *Drug* 1976; 11(1):86-90.
- Baekeland F, Lundwall L. Dropping out of treatment: a critical review. *Psychological Bulletin*; 82 (5): 738-783.
- Bailey WC, Richards JM, Brooks CM, et al. A randomized trial of strategies to improve patient compliance with anticonvulsant therapy. *Arch Intern Med* 1990; 150: 1664-68.
- Bandura A. Self-efficacy:toward a unifying theory of behavioral change. *Psychol Review* 1977; 84: 191-215.
- Bandura A. Self-referent thought: a developmental analysis of self-efficacy. In Flovell J, Ross L, editors. *Social Cognitive Development*. New York: Cambridge University Press; 1981. P. 200-239.
- Bandura A. S. Self-efficacy mechanism in human agency. *American Psychologist* 1982; 37:122-147.
- Becker MH. Patient adherence to prescribed therapies. *Med Care* 1985; 23: 539-555.
- Becker MH. Sociobehavioral Determinants of Compliance. In Sackett DL, Haynes RB, editors. *Compliance with Therapeutic Regimens*. Baltimore: The Johns Hopkins University Press; 1976. p. 40-50.
- Becker MH, GreenA family approach to compliance with medical treatment: a selective review of the literature. *International Journal of Health Education* 1975; 18 (3): 173-182.
- Becker MH, Maiman LA, Kirscht JP, Haefner DP, Drachman RH, Taylor DW. Patient Perceptions and Compliance: Recent Studies of the Health Belief Model. In Haynes RB, Taylor DW, Sackett DL, editors. *Compliance in Health Care*. Baltimore: The Johns Hopkins University Press; 1979. p.78-109.
- Becker MH, Maiman LA. Sociobehavioral determinents of compliance with health and medical care regimens. *Medical Care* 1975; 13: 10-24.
- Becker MH, Maimain LA. Strategies for enhancing patient compliance. *Journal of Community Health* 1980; 6: 113-135.
- Bennett M; Indyk D, Golub S. Adherence re-framed in the BIG picture: A qualitative ecological perspective on HIV+ patients and protease inhibitors. Abstract at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Bond GR, Miller L, Krumweid R, Ward R. Assertive case management in three CMHCs: A controlled study. *Hospital and Community Psychiatry*. 1988; 39: 411-418.

Brand F, Smith R, Brand P. Effect of economic barriers to medical care on patients' noncompliance. *Public Health Rep* 1977; 92: 72-78.

Buchman WF. Adherence :a matter of self-efficacy and power. *Journal of Advanced Nursing* 1997 July; 26 (1): 132-137.

Bundek NI, Marks G, Richardson JL. Role of health locus of control beliefs in cancer screening of elderly Hispanic Women. *Health Psychology* 1993; 12: 193-199.

Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment and control of hypertension in the adult U.S. population. Data from the Health Examination Surveys, 1960 to 1991. *Hypertension* 1995; 26: 60-69.

Cameron K, Gregor F. Chronic Illness and Compliance. *Journal of Advanced Nursing* 1987; 12: 671-676.

AIDS falls from Top Ten Causes of Death; Teen Births, Infant Mortality , Homicide All Decline. *Health and Human Service News* (serial online). 1998 Oct 7. Available from URL <http://www.CDC.gov/nchswwww/releases/98news/98news/aidsmort.htm>

Charney E. Patient-doctor communication. *Pediatr Clin North America* 1972; 19:263.

Chesney M. Abstract # 281 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Clinite JC, Kabat HF. Prescribed drugs, errors during self-administration. *J Am Pharm Assoc* 1969; NS9: 450-452.

Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. *Science*. 1995; 267: 483-489.

Coffin JM. HIV viral dynamics. *AIDS* 1996; 10 supplement 3: s75-s84.

Colcher IS, Bass JW. Penicillin treatment of streptococcal pharyngitis. *JAMA* 1972; 222: 657-659.

Condra JH, Schleif WA, Blahy OM, Babryelski LJ, Graham DJ, Quintero JC et al. In vivo emergence of HIV variants resistant to multiple protease inhibitors. *Nature*. 1995; 374:569-571.

Conway B, Montessori B, Rouleau D, et al. Primary lamivudine resistance in acute HIV infection. In: Program and abstracts of the International Workshop on HIV Drug Resistance, Treatment Strategies, and Eradication; St. Petersburg, Fla; June 25-28, 1997. Abstract 103

Cooper GM, *The Cell; A Molecular Approach*. First edition. Washington, DC: ASM Publishers; 1997.

Cummings KM, Becker MH, Kirscht JP, Levin NW. Intervention strategies to improve compliance with medical regimens by ambulatory dialysis patients. *Journal of Behavioral Medicine* 1981; 4: 111-127.

Cummings KM, Becker MH, Kirscht JP, Levin NW. Psychosocial factors affecting adherence to medical regimens in a group of hemodialysis patients. *Med Care* 1982; 20: 567-580.

Davis M, Eichhorn RL. Compliance with medical regimens: A panel study. *J Health Hum Behavior* 1963; 4: 240-249.

Davis, M. Variations in patients compliance with doctor's advice: an empirical analysis of patterns of communication. *American Journal of Public Health* 1968; 58: 272.

Davis MS. Physiologic, psychological, and demographic factors in patient compliance with doctors orders. *Med Care* 1968; VI: 115-122.

Dunbar JM, Agras WS. Compliance with medical instructions. In: *Comprehensive Handbook of Behavioral Medicine*. Third edition. New York: Spectrum; 1980.

Dunbar-Jacob J, Dwyer K, Dunning EJ. Compliance with antihypertensive regimen: a review of the research in the 1980's. *Soc Behav Med* 1991; 13: 31-39.

Dunst C, Trivette C. An enablement and empowerment perspective of case management. *Topics of Early Childhood Special Education*. 1989; 8: 87-102.

Eiser JR, Eiser C, Gammage P, Morgan M. Health locus of control and health beliefs in realltion to adolescent smoking. *British Journal Addict* 1989; 84: 1059-1065.

Eraker SA, Kirscht JP, Becker MH. Understanding and improving patient compliance. *Ann Intern Med* 1984; 100: 258-268.

Erice A, Mayers DL, Strike DG, et al. Primary infection with zidovudine-resistant human immunodeficiency virus type 1. *N Engl J Med*. 1993; 328: 1163-1165.

Faberow NL. Non-compliance as indirect self-destructive behavior. In: Gerber KE, Nehemkis AM, and editors. *Compliance: The Dilemma of the Chronically Ill*. New York: Springer; 1986.

Fisher JD, Fisher WA. Changing AIDS-Risk Behavior. *Psychological Bulletin* 1992; 111: 455-474.

Fletcher SW, Appel FA, Bourgois M. Improving emergency room patient follow-up in a metropolitan teaching hospital:effect of a follow-up check. *N Engl J Med.* 1974; 291: 385-388.

Francis V, Korsch BM, Morris MJ. Gaps in doctor-patient communication. *N Engl J Med* 1969.

Frank E, Kupfer DJ, Siegal LR. Alliance not compliance: a philosophy of outpatient care. *Journal of Clinical Psychiatry* 1995; 56:11-16.

Friedland G, Williams A. Attaining Higher Goals in HIV Treatment: The Central Importance of Adherence. *AIDS* in press.

Friedman IM, Litt IF. Promoting adolescents compliance with therapeutic regimens. *Prevention in Primary Care.* 1986; 33: 955-972.

Gallant JE, Block DS. Adherence to antiretroviral regimens in HIV-infected patients:results of a survey among physicians and patients. *J Int Assoc Physicians AIDS Care* 1998; 4 (5): 32-35.

Gordis L. Methodologic Issues in the Measurement of Patient Compliance. In: Sackett DL, Haynes RB, editors. *Compliance with Therapeutic Regimens.* Baltimore: The Johns Hopkins University Press; 1976. P. 51-82.

Green LW, Levine DM, Deeds SG. Clinical traits of health education for hypertensive outpatients:design and baseline date. *Prev Med.* 1975; 4417-425.

Green LW, Levine DM, Wolle J, et al. Development of randomized patient education expeeriments with urban poor hypertensives. *Patient Counsel Health Education* 1979; 1: 106-111.

Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infections and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med.* 1997; 337: 725-733.

Harris MB, Bruner CG. A comparison of a self-control and a contract procedure for weight control. *Behav Res Ther* 1971; 9: 347-354.

Haynes RB, Sackett DL, Gibson ES, Taylor DW, Hackett BC, Roberts RS, Johnson AL. Improvement of medication compliance in uncontrolled hypertension. *Lancet* 1976; 1: 1265-1268.

Haynes RB, Taylor DW, Sackett DL,editors. *Compliance in Health Care.* Baltimore: Johns Hopkins University Press; 1979. p.1-7

Haynes RB. A critical review of the 'determinants' of patient compliance with therapeutic regimens. In Haynes RB, Taylor DW, Sackett DL, editors. *Compliance in Health Care*. Baltimore; The Johns Hopkins University Press; 1976:2: p. 9-25.

Haynes RB. Determinants of Compliance: The Disease and the Mechanics of Treatment. In Haynes RB, Taylor DW, Sackett DL, editors. *Compliance in Health Care*. Baltimore: Johns Hopkins University Press; 1979. P. 49-62.

Haynes RB, Wang E, Da Mota Gomes M. A critical review of interventions to improve compliance with prescribed medications. *Patient Education and Counseling* 1987; 10:155-166.

Haynes RB, McKibbin AK, Kanani Ronak. Systematic review of randomized trials of interventions to assist patients to follow prescriptions for medications. *The Lancet*. 1996; 348: 383-386.

Hecht F, Kahn JO, Dillon B, Chesney M, Grant RM. Transmission of protease inhibitor resistant HIV-1 to a recently infected antiretroviral-naïve man: The UCSF options primary HIV project. Abstract #32288 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Hemminki E, Heikkila J. Elderly people's compliance with prescriptions and quality of medication. *Scand J Soc Med* 1975; 3:87-92.

Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4⁺ lymphocytes in HIV-1 infection. *Nature*. 1995; 373: 123-126.

Ho D, Neumann A, Perelson A, Chen W, Leonard J, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995 Jan 12; 373: 123-126.

Holzemer WL, Inouye J, Brown MA, Powell GM, Corless IB, Turner JB, Nokes KM. Psychological well-being and HIV adherence. Abstract 32368 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Hulka BS. Motivation techniques in a cancer detection program. *Public Health Reports* 1966; 81: 1009-1014.

Hulka BS, Kupper LL, Cassel JC, Efrid RL, Birdette JA. Medication use and misuse: physician -patient discrepancies. *J Chronic Dis* 1975; 28: 7-21.

Hussey LC, Gilliland K. Compliance, Low Literacy, and Locus of Control. *Nursing Clinics of North America* 1989; 24; 3: 605-611.

Imrie A, Beveridge A, Genn W, et al. Transmission of human immunodeficiency virus type 1 resistant to nevirapine and zidovudine. *J Infect Dis.* 1997; 175:1502-1506.

Janz NK, Becker MH. The Health Belief Model: A Decade Later. *Health Education Quarterly.* 1984; 1-47.

Jiminez-Nacher I, Rodriguez-Rosado R, Anton P, Soriano AV, Gonzalez-Lahoz J. Virological failure and adherence to antiretroviral therapy in HIV infected patients. Abstract # 32350 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Johnston BE, Ahmed K, Smith C, Rose DN. Adherence to highly active antiretroviral therapy among HIV-infected patients of the inner city. Abstract # 32389 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Kasl SV. The health belief model and behavior related to chronic illness. *Health Education Monographs* 1974; 2: 433-455.

Kempf DJ, Rode RA, Xi Y, et al. The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. *AIDS* 1998; 12:F9-F14.

Kirscht JP, Kirscht JL, Rosenstock IM. A test of interventions to increase adherence to hypertensive medical regimens. *Health Educ Q* 1981; 8: 261-272.

Kirscht JP, Rosenstock IM. Patient adherence to antihypertensive medical regimens. *J Community Health.* 1977; 3:115.

Latiolais CJ, Berry CC. Misuse of prescription medications by outpatients. *Drug Intell Clin Pharm* 1969; 3:270-277.

Levine DM, Green LW, Chwalow AJ, et al. Health education for hypertensive patients. *JAMA.* 1979; 241:1700-1703.

Logan AG, Milne BJ, Achber C, Campbell WP, Haynes RB. Work site treatment of hypertension by specially trained nurses. *Lancet* 1979; ii: 1175-1178.

Maiman LA, Green LW, Gibson G, Mackenzie EJ. Education for self-treatment by adult asthmatics. *JAMA* 1979; 241:1919-1922.

Malahy B. The effect of instruction and labeling on the number of medication errors made by patients at home. *Am J Hosp Pharm* 1966; 23:283-292.

Markowitz M. Eradication of Rheumatic fever: An unfilled hope. *Circulation* 1970 41: 1077-1084.

Martin GA, Worthington EL Jr. Behavioral homework. In: Progress in behavior modification. New York: Academic Press; 1980.

Mayers DL, Yerly S, Perrin L, et al. Prevalence and clinical course of persons seroconverting with AZT-resistant (AZT sup R) HIV-1 in Switzerland, Australia, and the United States between 1988 and 1994. AIDS Res Human Retroviruses. 1995; 11(suppl 10):S162.

Mazzullo J. Methods of improving patient compliance. In: Lasagna L, ed. Patient Compliance. New York: Futura Publishing; 1976.

Mellors JW, Rinaldo CR, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 Infection Predicted by the Quantity of Virus in Plasma. Science 1996 May 24; 272: 1167-1170.

Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, Kingsley LA, Todd JA, Saah AJ, Detels R, Phair JP, Rinaldo CR. Plasma Viral Load and CD4+ Lymphocytes as Prognostic Markers of HIV-1 Infection. Ann Intern Med 1997 June 15; 126:946-954.

Meichenbaum D, Turk DC. Behavior modification approaches. In: Facilitating Treatment Adherence. New York: Plenum Press; 1987. p. 149-184.

Meichenbaum D, Turk DC. Factors Affecting Adherence. In: Facilitating Treatment Adherence. New York: Plenum Press; 1987. p. 41-68.

Miller NH, Taylor CB. Lifestyle management for patients with coronary heart disease. Current Issues in Cardiac rehabilitation, 1995; monograph 2.

Molla A, Korneyeva M, Gao Q, et al. Ordered accumulation of mutations in HIV protease inhibitors. Nature 1995; 374: 569-571.

Nakashima AK, Jones JL, Burgess DA, Ward JW. Adherence to currently prescribed antiretroviral therapies: Results from a multisite interview project. Abstract # 393/32326 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Neely E, Patrick ML. Problems of aged persons taking medications at home. Nurs Res 1968; 17: 52-55.

Oakes TW, Ward JR, Gray RM, Klauber MR, Moody PM. Family expectations and arthritis patient compliance to a hand resting splint regimen. Journal of Chronic Diseases 1970; 22: 757-764.

O'Brien MK, Petrie K, Raeburn J. Adherence to medication regimens: Updating a complex medical issue. Med Care Rev 1992; 49:435-454.

Parkin DM, Henney CR, Quirk J, Crooks J. Deviation from prescribed drug treatment after discharge from hospital. *Br Med J* 1976; 2: 686-688.

Parson T. On becoming a patient. In Foltz JF, Deck ES, editors. *A Sociological Framework for Patient Care*. New York: John Wiley & Sons. p. 246-252.

Porter AMW. Drug defaulting in a general practice. *British Medical Journal* 1969; 1:218-222.

Pratt JH, Jones JJ. Noncompliance with therapy: an ongoing problem in treating hypertension. *Primary Cardiology* 1995; 21: 34-38

Prochaska J, DiClemente C. Stages and processes of self-change of smoking: Toward an integrative model of change. *Journal of Consulting and Clinical Psychology* 1983;51: 390-394.

Prochaska JO, Redding CA, Harlow LL, Rossi JS, Velicer WF. The Transtheoretical Model of Change and HIV Prevention: A Review. *Health Education Quarterly* 1994; 21: 471-486.

Prochaska JO, DiClemente CC. Stages and processes of self-change in smoking: Towards an integrative model of change. *J Consult Clin Psychol* 1991; 59: 259-304.

Quigg M, Rebus S, France AJ, McMenamin J, Darby G, Leigh Brown AJ. Mutations associated with zidovudine resistance in HIV-1 among recent seroconvertors. *AIDS*. 1997; 11:835-836.

Quirk J, Wilks J. Patient compliance on combination HIV anti-retroviral therapies. Abstract # 32384 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Rapp CA. The Purpose, Principles, and Research Results of the Strengths Model. In: *The Strengths Model: Case Management with People Suffering from Severe and Persistent Mental Illness*. New York: Oxford University Press; 1998: p. 44-60.

Redeker NS. Health beliefs and adherence in chronic illness. *Image: Journal of Nursing Scholarship* 1988; 20: 31-35.

Redeker NS. Health beliefs, health locus of control, and the frequency of breast self-examination in women. *J Obstetrical Gynecol Neonatal Nursing* 1989; 18: 45-51.

Rodriguez-Rosado R, Jimenez-Nacher I, Soriano V, et al. Virological failure and adherence to antiretroviral therapy in HIV-infected patients. *AIDS* 1998; 12 (9):1112-3.

Rosenberg SG. Patient education leads to better care for heart patients. *Health Rep*

1971; 86: 793-802.

Rosenstock IM. Historical Origins of the Health Belief Model. Health Education Monographs. 1974; 2: 4: 328-335.

Rothman J. Guidelines for case management: Putting research to professional use. Itasca, Illinois: F.E. Peacock Inc; 1992

Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: A Meta-Analysis. Medical Care 1998; 36 (8): 1138-1161.

Rudd p. Clinicians and patients with hypertension: unsettled issues about compliance. Am Heart J 1995; 130:572-579.

Sackett DL, Snow JC. The magnitude of compliance and non-compliance. In Haynes RB, Taylor DW, Sackett DL, editors. Compliance in Health Care. Baltimore; The Johns Hopkins University Press; 1979;2: p. 9-25.

Svarsted BL. Physician-patient communication and patient conformity with medical advice. In: Mechanic D, Ed. The Growth of Bureaucratic Medicine: An inquiry into the Dynamics of Patient Behavior and the Organization of Medical Care. New York; John Wiley and Sons; 1976: p220-238.

Schapiro JM, Winters MA, Stewart F, Efron B, Norris J, Kozal MJ, Merigan TC. The effect of high-dose Saquinavir on viral load and CD4+ T-cell counts in HIV infected patients. Ann Intern Med 1996; 124: 1039-1050.

Schwartz S., Goldman H, and Churgin S. Case management for the chronic mentally ill: Models and dimensions. Hospital and Community Psychiatry. 1982; 33: 1006-1009.

Segal S, Avirim U. The mentally ill in community based sheltered care: A study of community care and social integration. New York: John Wiley and Sons; 1978.

Strang JS, Falloon IRH, Moss HB, Razani J, Boyd JL. The effects of family therapy on treatment compliance in schizophrenia. Psychopharmacol Bull 1981; 17: 87-88.

Strauss AL, Corbin J, Fagerhaugh S, Glaser BG, Maines D, Suczer B, Weiner CL. Chronic Illness and the Quality of Life, St. Louis: 2nd edition:, CV Mosby; 1984.

Taylor DW, Sackett DL, Haynes RB, Johnson AL, Gibson ES, Roberts RS. Compliance with antihypertensive drug therapy. Annals of the New York Academy of Sciences. 1978; 304: 390-403.

Test MA, Stein LI. Alternatives to mental hospital treatment, III. Social cost. Archives of General Psychiatry. 1980; 37: 409-412.

Vincent P. Factors influencing patient non-compliance: A theoretical approach. *Nursing Research*. 1971; 20: 509-516.

Wainberg M, Friedland G. Public Health Implications of Antiretroviral Therapy and HIV Drug Resistance. *JAMA*. 1998; 279: 1977-1983.

Walsh J; M Dalton; J Gill; D Wilkinson, AP Burgess; BG Gazzard. Adherence to Proteinase inhibitor based Highly Effective Antiretroviral Therapy (HEART). Abstract # #12298 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Wei X, Ghosh SK, Taylor ME, Johnson VA. Emini EA, Deutsch P, Lifson JD, Bonshoeffter S, Nowak MA, Hahn BH, Saag MS, Shaw GM. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 1995 Jan 12; 373: 117-22.

Weintraub M , AU WY, Lasagna L. Compliance as a determinant of serum digoxin concentration. *JAMA* 1973; 224:481-485.

Williams A, Wolf H, Yu C, Singh M. Adherence to antiretroviral therapy among HIV positive women. Abstract # 32374 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

Wong, JK, Hezareh M, Gunthard, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. *Science* 1997; 278: 1291-1295.

Woodward J, Wareham PS, Grohskopf L, Madigan D, Hooton TM. Protease Inhibitor adherence and HIV-1 RNA response.. Abstract # 60363 presented at the 12th World Conference on AIDS; 1998 June 28-July 3; Geneva, Switzerland.

